Potassium *tert*-Butoxide in Synthesis

D. E. PEARSON† and CALVIN A. BUEHLER*

Departments of Chemistry, Vanderbilt University, Nashville, Tennessee 37235, and University of Tennessee, Knoxville, Tennessee 37916

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† Vanderbilt University.
* Author to whom correspondence should be addressed, University of Tennessee.

I. Introduction

The increasing popularity of potassium *tert*-butoxide as a base catalyst has prompted the authors to review uses of this reagent in synthesis. The reactions are presented in a systematic manner with no attempt to include all examples; rather one or several, which are typical of each type of reaction, are given. Wherever comparisons of potassium *tert*-butoxide are made with other bases, they have been included in the discussion of the reaction. Unfortunately, the comparisons are limited in number.

The panorama of base-catalyzed reactions by *tert*-butoxide is large enough for the reader to find precedent for most reactions of interest, but interest will be enhanced if he is mindful of certain conclusions which emerge from the plethora of data. The base strength of *tert*-butoxide (or of any other base) is dependent on the solvent in which it is dissolved; it is greatest in dimethyl sulfoxide and smallest in benzene or other nonpolar solvents; it is relatively weak in *tert*-butyl alcohol as well. Reasons are elaborated in section II of this review. Base strength variability complicates the difficulties in making comparisons of *tert*-butoxide with other alkoxides. In many cases the alkoxides must be interchangeable, but the convenience of using commercial *tert*-butoxide free from solvation, its stability in storage, its structural lack of α hydrogen atoms for self-deprotonation, its lesser tendency to undergo SN2 reactions to form *tert*-butyl ethers, and, in some cases, its versatile range of base strength (controlled by solvent selection) contribute to its increasing popularity.

The *tert*-butoxide is a new reagent, its first use having been recorded about 25 years ago. In the review the literature is covered through 1971 with several references in early 1972. The only review now available appears to be that of Fieser and Fieser.[1] Our treatment is somewhat more comprehensive, a trait which we believe is justified in view of the increasing importance of the reagent.

Abbreviations used in the manuscript are the following.

Am	Amyl
Bu	Butyl
t-BuOH	*tert*-Butyl alcohol
t-BuOK	Potassium *tert*-butoxide
DCC	Dicyclohexylcarbodiimide
Diglyme	Di(ethylene glycol) dimethyl ether
DHN	Decahydronaphthalene
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DME or glyme	1,2-Dimethoxyethane
Et	Ethyl
HMPA	Hexamethylphosphoramide
Me	Methyl
Ms	Mesyl
NBS	*N*-Bromosuccinimide
Ph	Phenyl
Pr	Propyl
i-Pr	Isopropyl
THF	Tetrahydrofuran
TMU	Tetramethylurea
Ts	Tosyl

II. The Reagent

A. Preparation and Purification

Potassium *tert*-butoxide is now available commercially (MSA Research Corp., Evans City, Pa. 16033). The most detailed literature preparations appear to be those of Johnson[2] and Skattebøl.[3] By these procedures the *tert*-butoxide is prepared under nitrogen in the same container in which it is later used in a reaction. The best method of purification is by sublimation[4,5] [220° (1 mm) or 180° (0.05 mm)]. Under these conditions the product was obtained over 99.8% pure (titration).

When first received from the manufacturer, the *tert*-butoxide can be sublimed in an 85–95% yield. The purity, however, gradually declines as the original contents are stored in a desiccator if the container is occasionally opened. After a year or so of such treatment, the purity may fall to as little as 30%. This result suggests two precautions: first, the manufacturer should use an efficiently sealed bottle; second, the user should employ a freshly sublimed product in any crucial experiment. The best practice is to remove the *tert*-butoxide from the sublimer in a drybox or, more simply, in a polyethylene glove box kept inflated by nitrogen and then to transfer it in the same environment to a weighing bottle with a lightly greased ground-glass lid. Because of the pronounced tendency of the *tert*-butoxide to absorb components from the air, there seems little doubt that some experiments in the past have failed because the alleged *tert*-butoxide contained high percentages of carbonate and hydroxide.

B. Physical and Chemical Properties

Potassium *tert*-butoxide is a white, hygroscopic solid. The usual impurities are potassium hydroxide and potassium carbonate, both of which remain as a residue upon sublimation. Unfortunately, the appearance of the impure differs little from the pure product. The solubility of the oxide is given in Table I.

As has already been intimated, the reactions involving the *tert*-butoxide should be conducted in an inert atmosphere, usually nitrogen. *The substance attacks the skin and may ignite upon exposure to air or oxygen at elevated temperatures.*

From a practical point of view the *tert*-butoxide can be considered to be a strong base, stronger than primary and secondary alkoxides, but much weaker than sodamide and its derivatives. It can also be considered as a relatively poor nucleophile, but one which to some extent favors proton abstraction over displacement by or addition of an anion. Yet it is neither the best base nor the poorest nucleophile available. Its popularity must then stem from its commercial availability and the fairly good range of basicities which it offers. This range from strongest to weakest is as follows: *t*-BuOK in DMSO (near monomeric) > *t*-BuOK, neat > *t*-BuOK in C_6H_5R (probably a tetramer in C_6H_6[6]), or THF > *t*-BuOK in *t*-BuOH (1:1 complex is known[7]).

TABLE I. Solubility[a] of *t*-BuOK in Organic Solvents

Solvent	Solubility, g/100 g (25-26°)
Hexane	0.27
Toluene	2.27
Ether	4.34
t-BuOH	17.8
THF	25.00

[a] Reference 4.

For maximum basicity of *t*-BuOK, the DMSO in which it is dissolved should be scrupulously dry. Coetzee and Ritchie[8] recommend vacuum distillation of DMSO below 50° from AW-500 molecular sieves followed by distillation from sodamide at 40° or lower. Since for ordinary syntheses this purification is too elaborate, many chemists resort simply to distillation from calcium hydride under reduced pressure.

Comparative basicities may be estimated from the pK_a's[9,10] which follow: H_2O, 15.7; CH_3OH, 15.1; C_2H_5OH, 18; *i*-C_3H_7OH, 17.1; *t*-C_4H_9OH, 19 or more; DMSO, 23; $C_6H_5CH_3$, 35. These values deserve comment because they substantiate our ideas on the variability of the basicity of *t*-BuOK and for that matter of all bases. From inductive influences methanol should be a weaker acid than water, but the sequence above shows the opposite to be true. The reason is that in the equilibrium

$$\begin{array}{ccc} ROH & \rightleftharpoons & RO^- + H^+ \\ & & \mathbf{1} \\ & & \updownarrow ROH \\ & & \overset{\ominus}{[RO]}_n[ROH]_m \\ & & \mathbf{2} \end{array} \quad (1)$$

the cluster anion (**2**) as well as the monomeric anion (**1**) must be taken into account in determining the extent of the reverse reaction to give ROH. Evidently the cluster for the methoxide (R = CH_3) is less capable than that of the hydroxide (R = H) in reacting with the proton so that methanol appears to be more dissociated than water. Another manifestation of the influence of the cluster on dissociation is the latter's variability with solvents. In nonpolar solvents, clustering is at a maximum and ability to react with a proton is at a minimum. In DMSO clustering of the base is at a minimum and the ability to react with a proton is at a maximum. That is why *t*-BuOK in dry DMSO stands at the top of the list for obtaining the most basic form of the *tert*-butoxide.

The cluster of *t*-BuOK in THF is estimated to consist of four molecules of the monomer (neglecting molecules of *t*-BuOH and THF),[6,11] and yet it behaves in rate studies as though it were smaller, *i.e.*, a mixture of smaller and larger clusters averaging four.

The comparison of dissociation constants substantiates the claim that *t*-BuOK is a stronger base than the alkoxides of primary and secondary alcohols. The constant for DMSO suggests that a finite amount of dimsylpotassium

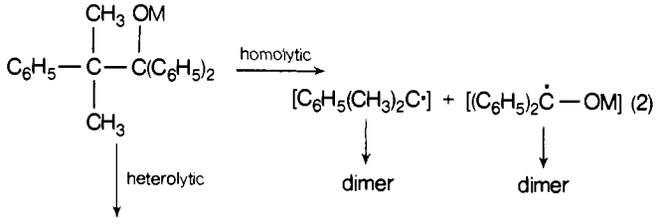
is present when *t*-BuOK is added to DMSO, a suggestion which has been confirmed.[12] The constant for toluene suggests an extremely small amount of exchange. Yet, even though the exchange is infinitely small, this minute amount is sufficient to bring about the replacement of hydrogen by deuterium at a surprisingly fast rate ($t_{1/2}(30°)$ = 41 min).[13] In other cases *t*-BuOK in DMSO is so active in forming carbanions that temperatures may be lowered 100–150° to obtain rates comparable to those obtained with the oxide in *t*-BuOH.[14]

The rates of base-catalyzed isomerization of alkenes have led to some interesting conclusions on the strength of bases.[15] The *tert*-butoxide is more effective in pure DMSO than in DMSO–THF, HMPA, or TMU. It is very ineffective in diglyme. It is superior to any other base in HMPA except certain lithium amides. The rates of isomerization appear to be proportional to the rates of proton removal.

The larger the cation in metal *tert*-butoxides the greater is the ionic character of the base and the faster is the rate of isomerization produced; *e.g.*, for the isomerization of 1- to 2-butene, *t*-BuOCs gives four times the rate of *t*-BuOK. On the other hand, *t*-BuOLi leads to a rate slower by a factor of ~1000 than *t*-BuOK.

Rates of racemization of an optically active hydrocarbon are 10^6 to 10^7 times faster with *t*-BuOK in *t*-BuOH–DMSO than in *t*-BuOH and 10^{13} faster than with MeOK in MeOH.[16]

The order of increasing covalency with the size of the counterion is $C_6H_5CH_2N^+Et_3 < K^+ < Na^+$. Presumably *t*-BuOLi is the most covalent base.[17] These differences between counterions are much smaller when measured in *t*-BuOH rather than in DMSO[14] because of the clustering of the bases in *t*-BuOH. The use of the counterion effect in DMSO is demonstrated[18] in eq 2 and 3. With *t*-



BuOK the ratio of heterolytic to homolytic splitting is 2.2, with *t*-BuONa it is 1.6, and with *t*-BuOLi it is 0.05. In some cases sulfolane is superior to DMSO in increasing the apparent basic strength of *t*-BuOK, but in other cases the reverse is true. For instance, DMSO is a better scavenger of methanol (by hydrogen bonding) than sulfolane,[16] and perhaps more examples will show that DMSO is superior only when the product formed is capable of hydrogen bonding. Sulfolane, on the other hand, is superior when the product cannot form hydrogen bonds.

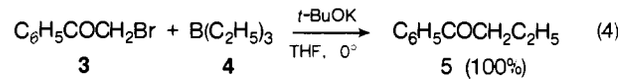
Other interesting points to bear in mind may be enumerated. The dielectric constant of *tert*-butyl alcohol is 11.2 at 30°, and it decreases with increasing temperature to the extent that the apparent basicity of the *tert*-butoxide in the alcohol is roughly halved at 50°.[17] Phenyllithium has been prepared in 77% yield from an equimolecular mixture of the *tert*-butoxide and *n*-butyllithium in benzene at room temperature,[19] perhaps as a result of an alteration in the size of the butyllithium cluster. In the following discussion the results will be rationalized in terms of the characteristics of the *tert*-butoxide described, but the reader will soon discover that all the mysteries of the base have not been unraveled as yet.

III. Alkylation or Arylation

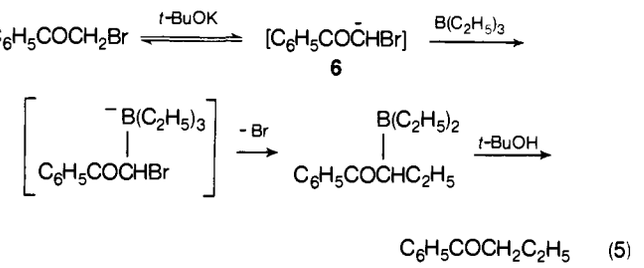
A. Ketones

1. α-Bromo Ketones and Boranes

The most thorough investigation of the α-alkylation of simple ketones is that of Brown and coworkers.[20] These investigators treated the α-bromo ketone **3** with the trialkylboron **4** and the *tert*-butoxide to obtain the alkylated ketone **5** in superior yield (eq 4). In this procedure

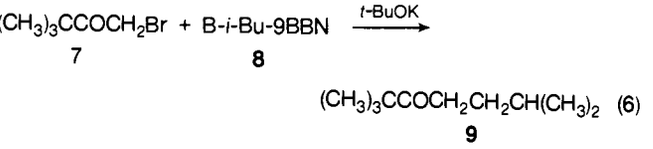


alkylation probably occurs through the carbanion **6** by the steps in eq 5.

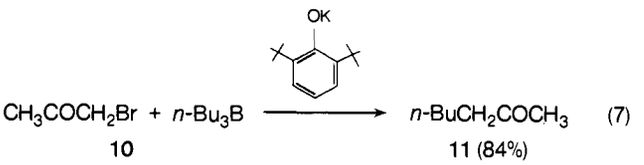


The *t*-butoxide in *t*-BuOH gives only a 25% yield with evidence of self-condensation of the bromo ketones as a side reaction. This method eliminates the concurrent formation of polyalkyl derivatives, which is characteristic of alkylation with sodamide and the alkyl halide. There are two principal objections to the method: since the organoborane is prepared from the olefin and since in monoalkylation only one alkyl group is introduced, a loss of the olefin results and the yield is not satisfactory for branched-chain organoboranes.

To overcome these difficulties Brown and coworkers[21] developed a new organoborane, *B*-alkyl-9-borabicyclo[3.3.1]nonane [B-R-9-BBN], which permits all of the olefin to be used and which gives reasonable yields when the alkyl group is branched. Thus the bromo ketone **7** with the isobutylnonane **8** gives a 61% yield of alkylated ketone **9**.

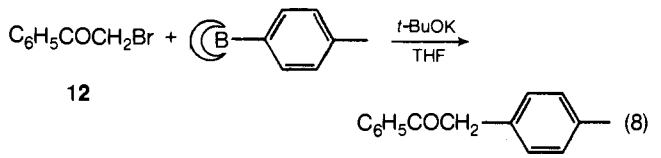


Unfortunately when the *tert*-butoxide is employed, the reaction is quite sensitive to the structure of the α-halo ketone. It fails, for example, when α-bromoacetone is the starting material. To solve this difficulty, Brown and coworkers[22] used the weaker base potassium 2,6-di-*tert*-butylphenoxide, which with bromoacetone **10** gives *n*-amyl methyl ketone (**11**) (eq 7). Thus the synthesis of methyl ketones by this method became a reality.



The α-arylation of ketones has been accomplished by the use of the *tert*-butoxide and *B*-aryl-9-borabicyclo-

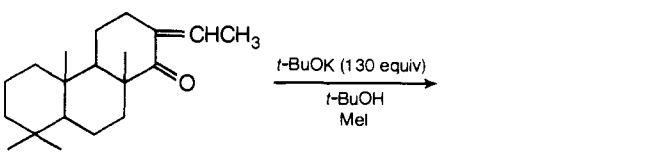
[3.3.1]nonanes.[23] In this manner the bromo ketone **12** yields the *p*-methylbenzyl ketone (**13**) (eq 8).



12 **13** (95%) (8)

2. *Ketones and Alkyl Halides or Diphenyliodonium Chloride*

Ketones may also be alkylated by an alkyl halide in the presence of the *tert*-butoxide. Sometimes a large excess of the *tert*-butoxide is needed to ensure complete enolization of the ketone,[24] as in the conversion of (±)-13-ethylidene-14-podocarpanone (**14**) into the methyl derivatives **15** (eq 9). Indeed the *tert*-butoxide is the reagent of choice for the formation of reductones (**16**) by enolization[25] (eq 10).



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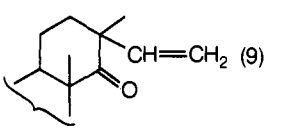
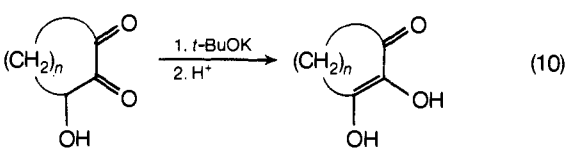
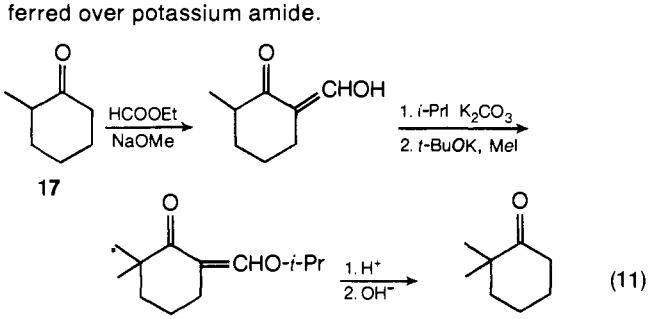


15 (32% equatorial) (9)



16 (10)

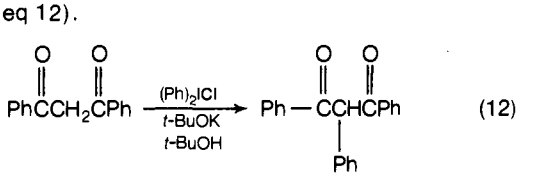
To direct the alkylation, the formyl derivative of the ketone may be employed. Thus Johnson and Posvic[26] obtained 2,2-dimethylcyclohexanone (**18**) from the methyl ketone **17** as in eq 11. Here the *tert*-butoxide was preferred over potassium amide.



17 **18** (32% overall) (11)

A similar alkylation of a ketone, cyclization to form an α-alkylamide, is given in section III.E.

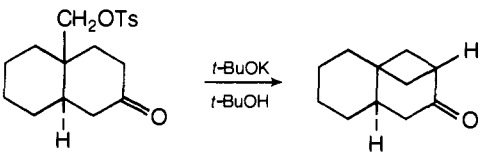
For arylation diphenyliodonium chloride is substituted for the alkyl halide. In this way Beringer and coworkers[27] arylated dibenzoylmethane (**19**) to obtain the phenyl derivative **20** (eq 12).



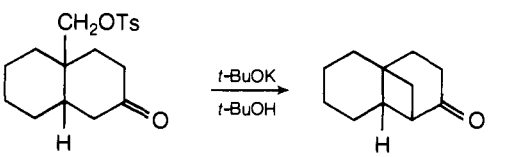
19 **20** (31%) (12)

3. *Tosylates of Ketobicyclic Alcohols (Intramolecular)*

An intramolecular alkylation to form new bonds leading to tricyclic systems occurs when the tosylates of ketobicyclic alcohols are treated with the *tert*-butoxide.[28] 10-Hydroxymethyl-2-oxo-*trans*-decalin tosylate (**21**) gives 4-oxotricyclo[4.4.1.0^{1,3}]undecane (**22**) (eq 13), while the cis form (**23**) gives 4-oxotricyclo[4.4.1.0^{1,5}]undecane (**24**) (eq 14).

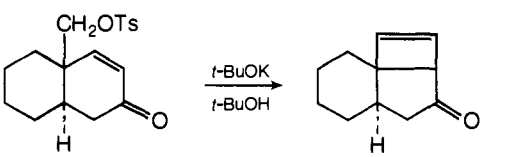


21 **22** (13)



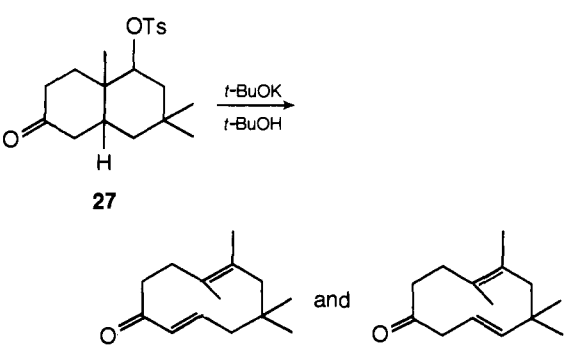
23 **24** (14)

10-Hydroxymethyl-$\Delta^{3,4}$-*trans*-2-octalone tosylate (**25**) leads to 5-oxotricyclo[5.4.0^{1,4}.0^{1,7}]undecene (**26**).



25 **26** (~50%) (15)

A series of rearrangements appears to follow the original ionization of **25.** In *cis*-6,6,9-trimethyl-8-tosyloxy-3-oxodecalin (**27**) one bond is broken and two double bonds are introduced to give a mixture of 7,7,10-trimethyl-3-oxo-4,9-cyclodecadiene and its $\beta\gamma$ isomer (**28**)[29] (eq 16).

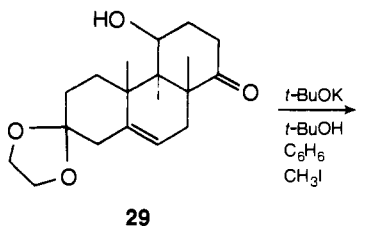


27 **28** (47%) (16)

B. Keto Steroids

The use of the *tert*-butoxide with the alkyl halide has become a common method for introducing alkyl groups in the α position of keto steroids. Sarett and coworkers[30] introduced one and two alkyl groups into 4b-methyl-7-ethylenedioxy-1,2,3,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (**29**) to acquire the mono (**30**) and dialkyl (**31**) derivatives (eq 17).

Later Woodward, Barton, and coworkers[31] produced 4,4-dimethylcholestenone (**34**) either from cholest-5-en-3-one (**32**) or cholest-4-en-3-one (**33**) by the same method (eq 18). In a similar manner Ireland and Schiess[24] converted 7-keto-1-methoxy-13-methyl-5,6,7,9,10,13-hex-



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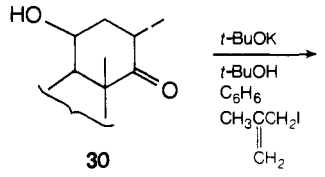

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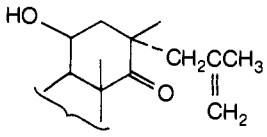
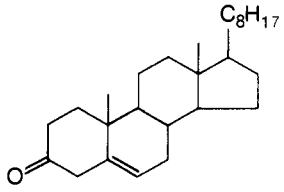


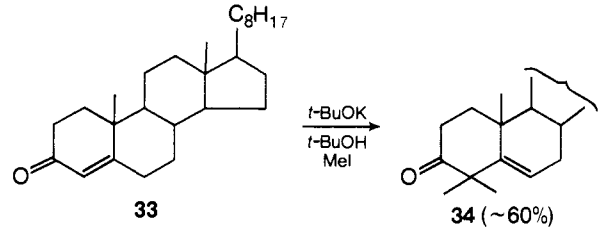
(17)

31



or

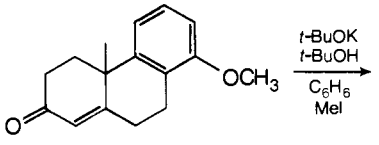
32



(18)

33 34 (~60%)

ahydrophenanthrene (**35**) into 7-keto-1-methoxy-8,8,13-trimethyl-5,6,7,8,10,13-hexahydrophenanthrene (**36**).



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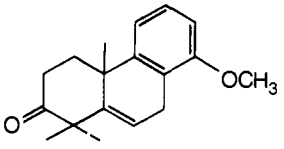


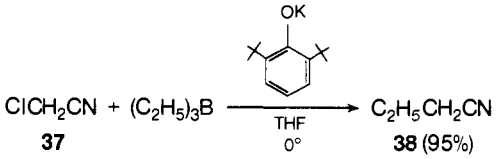
(19)

36 (75%)

C. Nitriles

1. α-Bromonitriles and Boranes

The Brown method of alkylation as applied to ketones (section III.A.1) may also be utilized in alkylating nitriles, provided potassium 2,6-di-*tert*-butylphenolate is substituted for the *tert*-butoxide.[32] The phenoxide is a weaker base, still capable of abstracting an α proton, but having less tendency to attack the nitrile group. The ethylation of chloroacetonitrile (**37**) by the use of this base to give butyronitrile (**38**) is given in eq 20.



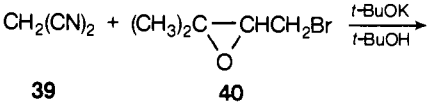
(20)

37 38 (95%)

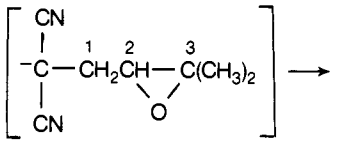
Again B-R-9-BBN may be employed instead of the trialkylborane if all of the original olefin is to be utilized in the reaction. Other nitriles prepared by this procedure are α-chlorobutyronitrile (89%), diethylacetonitrile (96%), ethyl α-ethylcyanoacetate[32] (91%), and α-ethylmalonitrile[33] (96%). By the use of B-Ar-9-BBN the α-arylation of chloroacetonitrile was accomplished[32] with a 75% yield.

2. Malonitrile and 1-Bromo-3-methyl-2,3-epoxybutane

Apparently strong bases tend to transform the nitrile to the imino group. For this reason alkylation with alkyl halides is rarely used for nitriles. One example is the alkylation of malonitrile[34] (**39**) with 1-bromo-3-methyl-2,3-epoxybutane (**40**) in the presence of the *tert*-butoxide to obtain, *via* the carbanion **41**, the α-iminolactone of 2-α-hydroxyisopropyl-1-cyano-1-cyclopropanecarboxylic acid (**42**) (eq 21).



39 40



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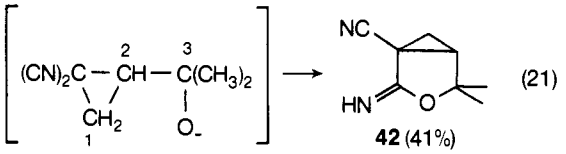
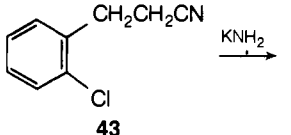


(21)

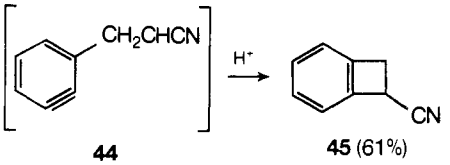
42 (41%)

3. (2-Chlorophenyl)-2-propionitrile

Although other examples of the alkylation of nitriles with alkyl halides have not been found, an example of α-arylation, using the strong base potassium amide,[35] is known. 3-(o-Chlorophenyl)propionitrile (**43**) gives 1-cyanobenzocyclobutene (**45**), in all probability *via* the benzyne carbanion **44** (eq 22).



43



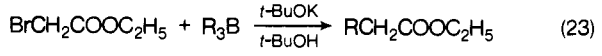
(22)

44 45 (61%)

D. Esters

1. α-Bromo Esters and Boranes

The Brown method of alkylation as applied to ketones (section III.A.1) and nitriles (section III.C.1) may also be utilized in the alkylation of esters.[36]



(23)

Since the organoborane is prepared from the olefin, it is possible to obtain the alkylated ester in one operation.

$$RCH{=}CH_2 \xrightarrow[3.\ t\text{-BuOK-}t\text{-BuOH}]{1.\ BH_3\text{-THF}\ 2.\ BrCH_2COOEt} RCH_2CH_2CH_2COOEt \quad (24)$$

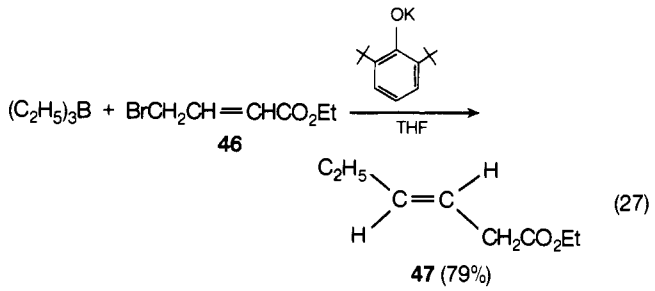
Yields starting with the olefin vary from 80 to 98%.

By employing dihalo esters and by using the proper amounts of the organoborane, it is possible to synthesize monobromo esters or α-dialkyl esters,[37] eq 25 and 26, respectively. In the latter case an alternative to the malonic ester synthesis becomes available. Again, as has been stated under the alkylation of ketones and nitriles, potassium 2,6-di-*tert*-butyl phenolate offers an advantage over the *tert*-butoxide in that an excess may be employed without decreasing the yield.[38] If all the original olefin is to be used in the reaction, B-R-9-BBN may be employed instead of the trialkylboron.

$$Br_2CHCOOC_2H_5 + R_3B \xrightarrow[t\text{-BuOH}]{t\text{-BuOK}} RCHBrCOOC_2H_5 \quad (25)$$
80–98%

$$+ 2R_3B \xrightarrow[t\text{-BuOH}]{t\text{-BuOK}} R_2CHCOOC_2H_5 \quad (26)$$
60–87%

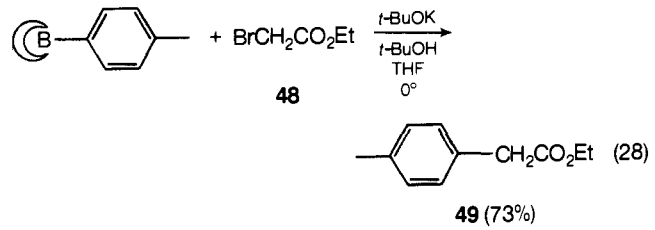
The use of the phenolate has permitted the completion of some reactions[39] not possible with the *tert*-butoxide. For example, the ethylation of ethyl 4-bromocrotonate (**46**) has been accomplished to give ethyl *trans*-3-hexenoate (**47**).



(27)

47 (79%)

The arylation of esters is successful through the use of the *tert*-butoxide and *B*-aryl-9-borobicyclo[3.3.1]-nonanes.[23] Thus ethyl *p*-tolylacetate (**49**) was prepared from ethyl bromoacetate (**48**).



(28)

49 (73%)

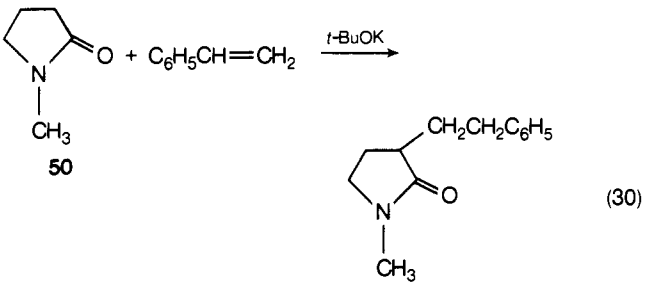
2. β-Keto Esters and Alkyl Halides

The advantage of using the *tert*-butoxide, particularly in the case of α-substituted esters, as the base in the alkylation of acetoacetic esters was pointed out first by Renfro and Renfro[40] (eq 29). The only failure occurred in the attempt to synthesize ethyl di-sec-butylacetoacetate.

$$CH_3COCHRCO_2Et \xrightarrow[R'I]{t\text{-BuOK}} CH_3COC(R)CO_2Et \quad (29)$$
R'

E. Amides (α-Alkylation)

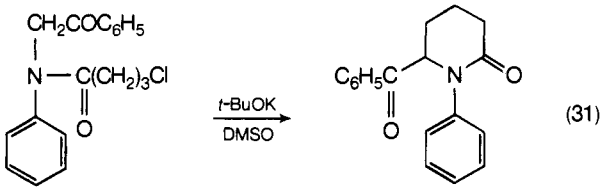
Pines and coworkers[41] discovered that *N*-methyl-2-pyrrolidinone and *N*-methyl-2-piperidone may be alkylated quantitatively in position 3 by the addition of styrene. Thus *N*-methyl-2-pyrrolidine (**50**) gives the 3-monoaddition product **51** (eq 30). Potassium *tert*-butoxide, neat, or in DMSO, may be used in the reaction and DMSO is superior to HMPA as a solvent. *N*-Methylcaprolactam could not be alkylated under these conditions. For successful results "it is imperative to use freshly sublimed *t*-BuOK."



(30)

51

The halogenated acylamino ketones and esters[42] undergo cyclization to form α-alkylamides. Thus the disubstituted aniline **52** gives the cyclic alkyl amide **53** (eq 31). The method is applicable when there are one, two, or three methylene groups in the substrate; thus it serves for the synthesis of piperidones, pyrrolidinones, and β-lactams, in which cases yields vary from 10 to 100%. Yields do not exceed those obtained with bases such as triethylamine, DMF, or anion-exchange resins, but the reaction time is shorter. In addition, the *tert*-butoxide is preferable to KOH in C_2H_5OH for the formation of β-lactams since the rings of the latter are cleaved by hydroxyl ions.



(31)

52 **53** (86%)

F. Amides (N-Alkylation)

1. 3-(*p*-Toluenesulfonamido)propyl *p*-Toluenesulfonate (to an Azetidide)

On refluxing 3-(*p*-toluenesulfonamido)propyl *p*-toluenesulfonate (**54**) with the *tert*-butoxide, Vaughan and coworkers[43] formed the azetidide **55** (eq 32). The maximum yield obtained using $NaOC_2H_5$ in C_2H_5OH was 80.7%.

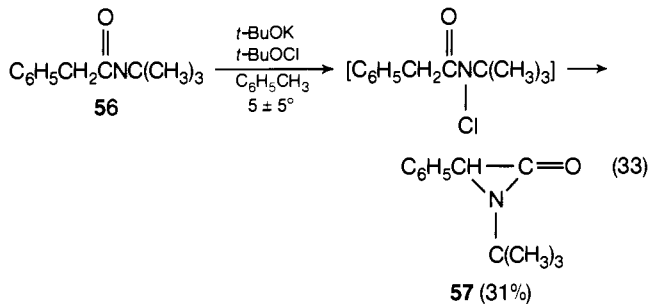
$$TsOCH_2CH_2CH_2NHTs \xrightarrow[t\text{-BuOH}]{t\text{-BuOK}} \text{N-Ts} \quad (32)$$
54 **55** (93%)

2. N-tert-Butylphenylacetamide (to an Aziridinone)

The first authentic aziridinone (α-lactam) was isolated by Baumgarten[44] in 1962. It (**57**) was synthesized from the amide **56** as shown in eq 33. To avoid ring opening the concentration of the *tert*-butyl alcohol was held to a minimum. For the synthesis of other aziridinones using the *tert*-butoxide, see the review of Lengyel and Sheehan.[45]

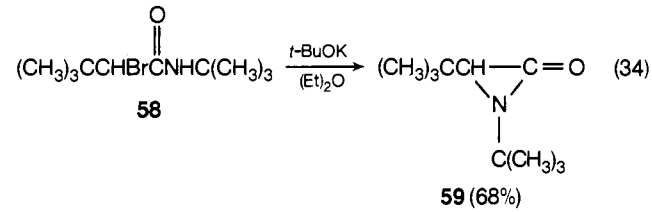
3. α- and β-Haloamides (to Aziridinones and Azetidinones)

To prepare an aziridinone (**59**), Sheehan and Beeson[46] prefer to start with the α-haloamide **58** (eq 34). 1,3-Di-



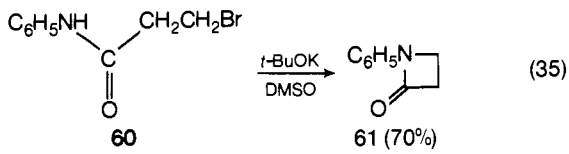
(33)

tert-butylaziridinone is unique in having a higher thermal stability and a lower chemical reactivity than the other known aziridinones.



(34)

A similar procedure to synthesize azetidinones (β-lactams) has been employed by Manhas and Jeng[47] who treated *N*-phenyl-β-bromopropionamide (**60**) as shown in eq 35, to acquire the azetidinone **61**. In this case, NaH in

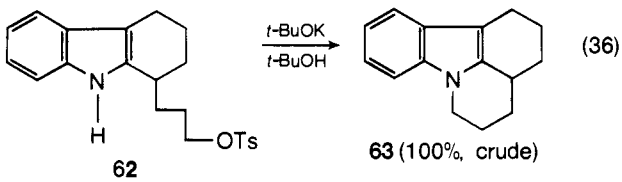


(35)

DMSO gave a higher yield (90%). It should be mentioned, however, that the *tert*-butoxide was used only in the example cited, while Na in liquid ammonia and NaH in DMSO were employed in many more examples.

4. A Tetracyclic Indole

Dolby and Esfandiari[48] succeeded in the N-alkylation of the tetrahydrocarbazole tosylate (**62**) to obtain the tetracyclic indole **63** (eq 36). Ethylmagnesium bromide gave a 90% yield (crude).



(36)

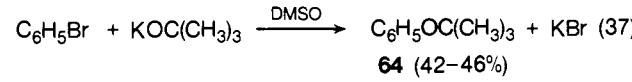
G. Alkoxides (to Form Ethers, Epoxides, Ketals, and Related Types)

Not only are alkoxylation reactions (RX + MOR' → ROR') included here but also some benzyne or strained alkyne reactions since both types of reactions frequently occur simultaneously. Benzyne formation, of course, is a dehydrohalogenation.

The *tert*-butoxide has not been used too frequently in the Williamson reaction because of its tendency to produce dehydrohalogenation. Indeed a better way usually to prepare *tert*-butyl ethers is *via* the Grignard reagent with *tert*-butyl perbenzoate.[49] Those reactions in which the *tert*-butoxide is satisfactory involve an yne intermediate.

1. Bromobenzene

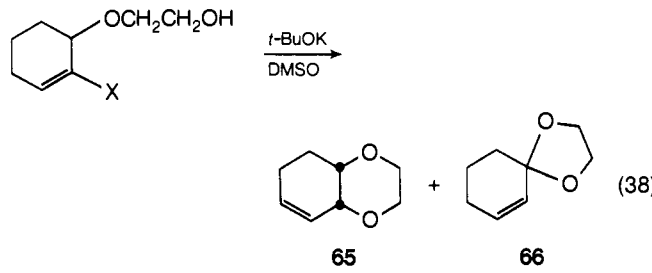
One of the earliest examples of ether preparation from an organic halide by the use of the *tert*-butoxide is that of phenyl *tert*-butyl ether[50] (**64**) (eq 37). Further examples are discussed in section VII.C.4.



(37)

2. 2-Halo-3-(2-hydroxyethoxy)cyclohexenes

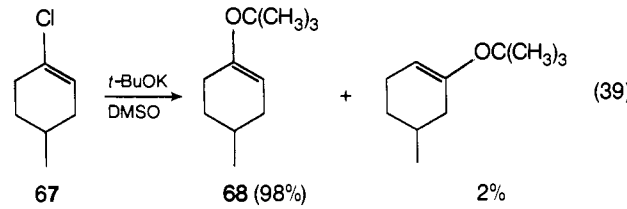
Treatment of the 2-halo-3-(2-hydroxyethoxy)cyclohexenes with the *tert*-butoxide leads to mixtures of *cis*-2,5-dioxabicyclo[4.4.0]dec-7-ene (**65**) and cyclohex-2-enone ethylene ketal (**66**)[51] (eq 38). When X = Br, 71%, consisting of nearly equal amounts of **65** and **66**, is obtained, while when X = Cl, the total yield is 42% with 92% being bicyclene and 8% ketal.



(38)

3. 1-Halo-4-methylcyclohexenes

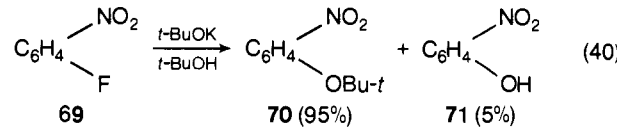
In a study of the reaction of 1-chloro-, 1-bromo-, and 1-iodo-4-methylcyclohexenes with the *tert*-butoxide in different solvents, Bottini and coworkers[52] found that the 1-ether is the main product, but that some of the 2-ether is also produced. The best yield of the 1-ether **68** is obtained from the 1-chlorocyclohexene **67** (eq 39). The results of the study are considered as being consistent not only with the intermediate formation of the cyclohexyne, but with the formation of the 1,2-cyclohexadiene as well.



(39)

4. o- and p-Fluoronitrobenzenes

To complicate the situation further, Pietro and Del Cima[53] found that the *tert*-butoxide with either o- or *p*-fluoronitrobenzene (**69**) gives respectively the yields of ortho or para ether **70** and o- or *p*-phenol **71** as stated in eq 40. These investigators regard the products as being formed by direct displacement since 3-nitrophenyl *tert*-butyl ether was not detected among the reaction products.



(40)

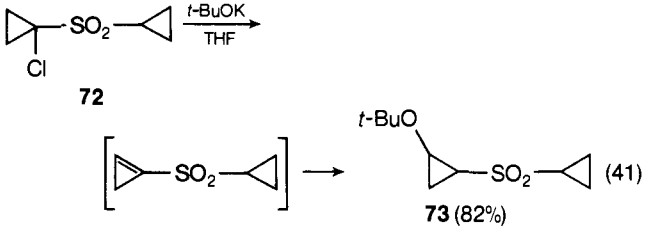
5. 1- and 2-Halonaphthalenes

1- and 2-Halonaphthalenes were treated with the *tert*-butoxide in a mixture of *t*-BuOH and DMSO[54] for short periods of time, and the amounts of products formed were determined by vpc analysis. The chief product was

the 2-*tert*-butyl ether (maximum 28 mol %), and 1,2-dehydronaphthalene was regarded to be the intermediate. Similarly the *tert*-butyl ether of cyclooctatetraene was obtained in 16% yield from the bromo derivative when it was treated with the *tert*-butoxide in ether.[55] Evidence for the intermediate formation of 1,2-dehydrooctatetraene was indicated by the formation of a Diels–Alder adduct.

6. α-Chlorocyclopropyl Cyclopropyl Sulfone

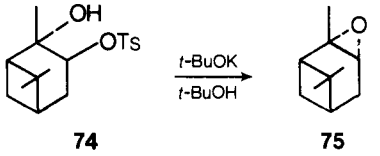
Paquette and Houser[56] subjected α-chlorocyclopropyl cyclopropyl sulfone (**72**) to the action of the *tert*-butoxide and obtained β-*tert*-butoxycyclopropyl cyclopropyl sulfone (**73**) (eq 41). As shown, cyclopropyl cyclopropenyl sulfone is regarded as the intermediate.



(41)

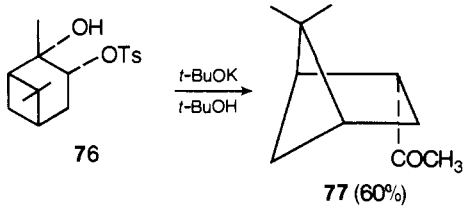
7. cis- and trans-2-Hydroxy-3-tosylpinane

Epoxides **75** have been produced by Carlson and Pierce[57] by treatment of α-*trans*-2-hydroxy-3-tosylpinane (**74**) with the *tert*-butoxide (eq 42). A similar reaction



(42)

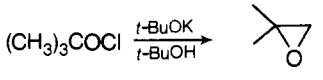
does not occur with the cis isomer **76.** Instead the ring contracted ketone 2-α-acetyl-5,5-dimethylbicyclo-[2.1.1]hexane (**77**) is obtained (eq 43). This experiment is cited as the first example of a chemical conversion of a pinane derivative into a bicyclo[2.1.1]hexane.



(43)

8. tert-Butyl Hypochlorite

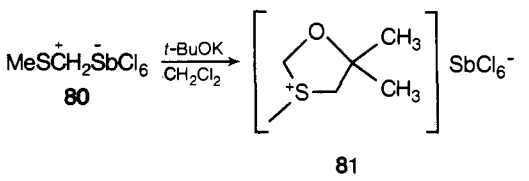
tert-Butyl hypochlorite (**78**) gives an epoxide[58] (**79**) (eq 44). The mechanism is a free radical one probably involving the intermediate $(CH_3)_2C(OH)CH_2Cl$.



(44)

9. Methylmethylene Sulfonium Hexachloroantimonate

On treating methylmethylene sulfonium hexachloroantimonate (**80**) with the *tert*-butoxide, Olofson and Hansen[59] obtained 3,5,5-trimethyl-1,3-oxathiolonium hexachloroantimonate (**81**) (eq 45). The reaction appears to involve the addition of **80** to isobutylene.

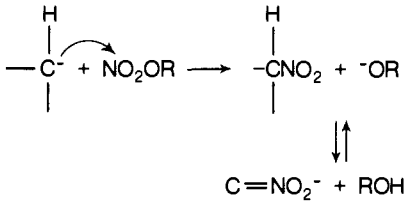


(45)

H. Nitrates and Nitrites

1. Nitrates

The *tert*-butoxide has been used extensively in the alkylation of nitrate esters by active methylene compounds.[60] The process may be represented by eq 46, or more specifically by eq 47–49. Some of the reactions



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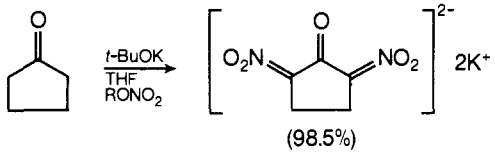

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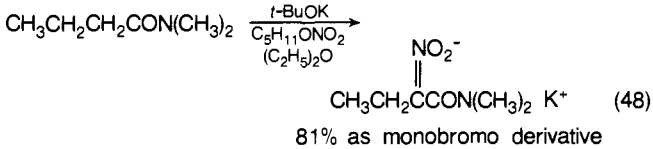

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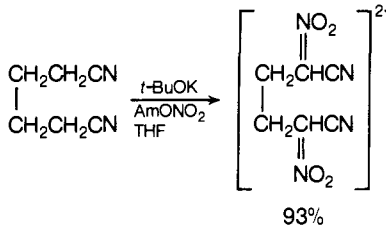
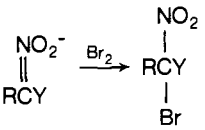


(49)

present difficulties because the products are normally hygroscopic and unstable, and often more than one product is obtained. For ease in handling, conversion of the product into the bromo derivative, eq 50, is common.

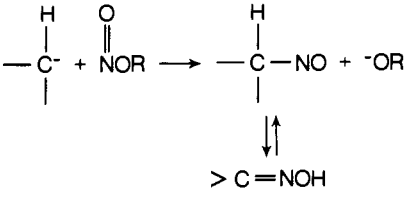


(50)

More recently Feuer, as a result of additional experimentation, has expressed a preference for the use of KNH_2 in liquid ammonia over the *tert*-butoxide in the alkylation of nitrates with cyclanones,[60e] α-nitrosulfonates,[61] and carboxylic esters.[60f]

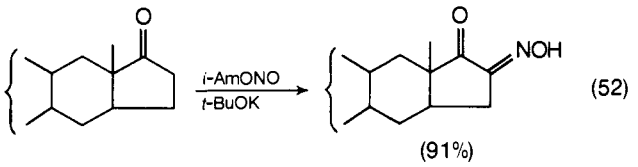
2. Nitrites

The alkylation of nitrite esters (eq 51) is similar in conditions to alkylation of nitrate esters. Although the use of



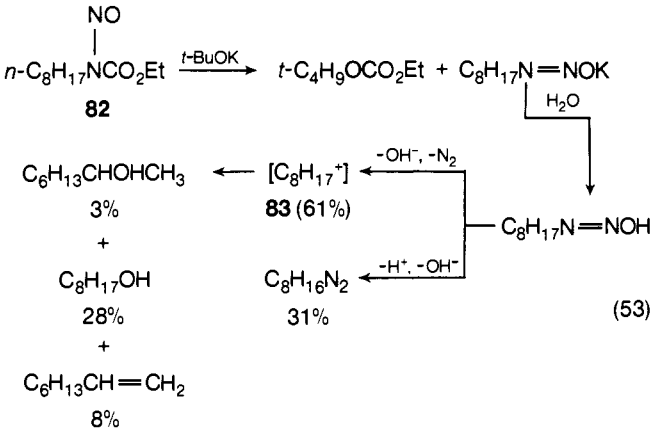
(51)

the ethoxide has been quite common in carrying out such alkylations,[62] the use of the *tert*-butoxide for alkylation with a steroid (eq 52) has been described.[63] Incidentally,



(91%) (52)

the *tert*-butoxide has a further use in nitroso chemistry. It can generate carbonium ions (**83**) from nitrosourethanes (**82**) in basic solution[64] (eq 53).

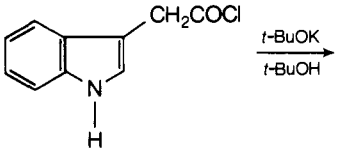


(53)

IV. Acylation and Solvolysis of Esters

A. Esterification

Barna[65] obtained a good yield of *tert*-butyl 3-indoleacetate (**85**) by treating the acid chloride (**84**) with the *tert*-butoxide (eq 54). The method is simpler than the reaction of the acid or anhydride with *tert*-butyl alcohol or transesterification.



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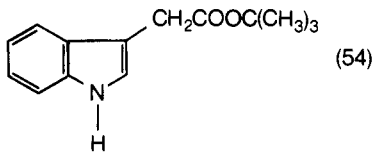
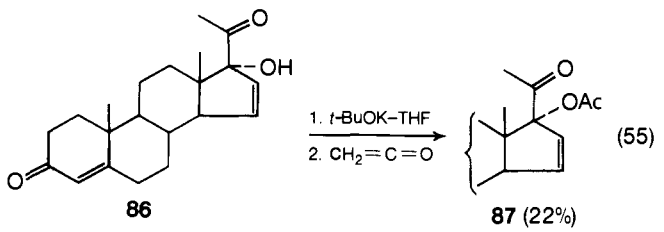


(54)

85 (81–90%)

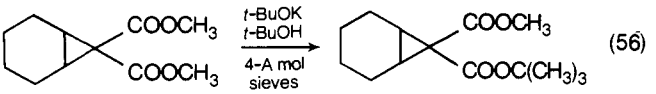
The acetylation of 17α-hydroxy-4,15-pregnadiene-3,20-dione[66] (**86**) to the acetate **87** has been accomplished with ketene (eq 55).



86 **87** (22%) (55)

B. Transesterification

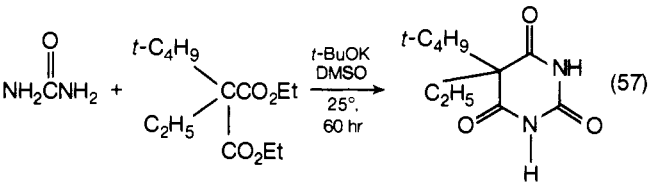
The large steric requirements of the *tert*-butoxide minimize transesterification, but a rather useful example has been found. The selective transesterification of the 7,7-dimethyl ester of norcarane (**88**) gives the methyl *tert*-butyl diester[67] (**89**) (eq 56). Without the molecular sieves the reaction stops at 80% conversion. The dimethyl ester of the 3-ene diacid gives a 94% yield of the mixed diester.



88 **89** (97%) (56)

C. Acylation of Urea

The anion of urea, formed readily by the *tert*-butoxide in DMSO, may be acylated by very hindered malonic esters[68] to lead to the barbiturate **90** (eq 57).



90 (20%) (57)

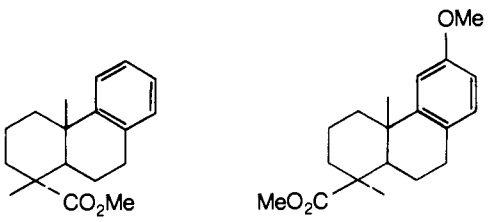
D. Solvolysis of Esters

1. Hindered Carboxylate Esters

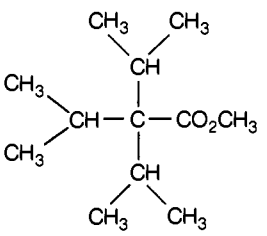
Although the solvolysis of esters is an alkylation of the *tert*-butoxide, it may also be regarded as the formation of an acid (as the salt), **92**, from the ester **91** (eq 58). Attention is drawn to the acid by this classification.

$$\underset{\textbf{91}}{RCO_2R'} + t\text{-BuOK} \longrightarrow \underset{\textbf{92}}{RCO_2^-} + K^+ + t\text{-BuOR}' \quad (58)$$

Chang and Wood[69] found that the *tert*-butoxide is of value in the hydrolysis of hindered esters. Previous reagents employed for the purpose were 100% sulfuric acid[70] (for 2,4,6-trialkylbenzoic acid esters), 18% hydrochloric acid[71] (for esters of sterically hindered acids and alcohols), lithium in liquid ammonia[72] (for axial carbethoxy esters in the diterpene field), lithium iodide in pyridine, 2,6-lutidine, or 2,4,6-collidine[73] (for certain acetoxy carboxylic acid methyl esters of the steroid and triterpene series), and lithium iodide in DMF[74] (for methyl glycyrrhetate). Chang and Wood on treating methyl dehydroabietate (**93**) with the *tert*-butoxide and DMSO for 1 hr at room temperature, followed by acidification, obtained a 94% yield of the free acid. Methyl *O*-methylpodocarpate



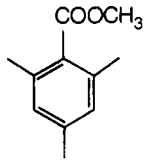
93 **94**



95

(**94**) treated similarly but at 56° for 2 hr gave a 97% yield of the corresponding acid. Methyl triisopropylacetate (**95**), being more resistant to hydrolysis, gave a nearly quantitative yield of acid only after 4 hr at 100°.

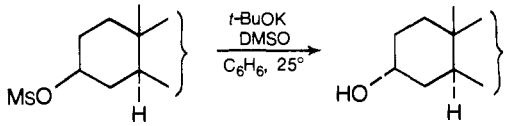
More recently Bartlett and Johnson[75] obtained excellent results by the use of lithium *n*-propyl mercaptide in HMPA at room temperature. With this reagent they acquired 100% of the free acid from methyl mesitoate (**96**) and from **94**, and 99% from **95**.



96

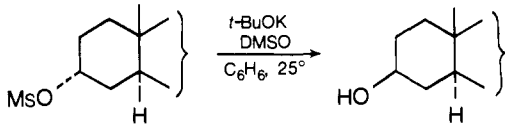
2. *Sterol Sulfonate Esters*

Although the alkaline hydrolysis of asymmetric sulfonate esters usually yields inverted or racemic alcohols, Chang[76] found that 3α-cholanol mesylate (**97**) (eq 59) and 3β-cholestanol mesylate (**98**) (eq 60) with the *tert*-butoxide gave good yields of the 3-alcohols without inversion. These results suggest that the *tert*-butoxide attacks the sulfur of the mesylate group. 3β-Cholestanol tosylate, 3α-cholestanol mesylate, and 3α-cholestanol tosylate gave largely olefins.



(59)

97 (87%)



(60)

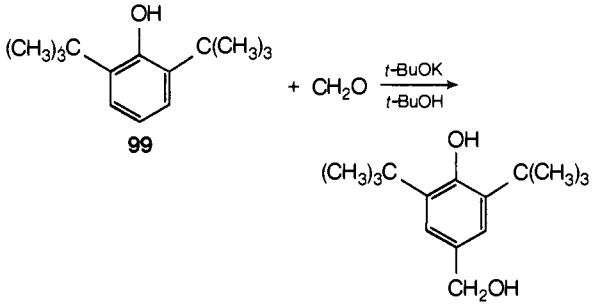
98 (86%)

V. Alkylolation or Alkenylation via Condensation

A. Aldol

Aldol condensations are brought about for the most part by mild alkaline or acidic catalysts. Sometimes, however, the condensation benefits from the use of the *tert*-butoxide. Three cases will be cited.

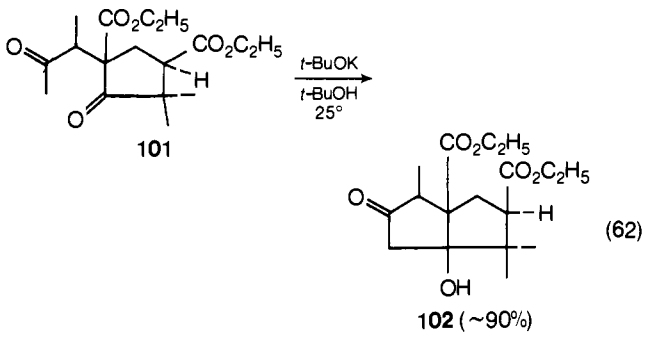
Methylolation occurs to give the benzyl alcohol (**100**) when 2,6-di-*tert*-butylphenol (**99**) and formaldehyde[77] are treated with the *tert*-butoxide (eq 61).



(61)

99 **100** (61–90%)

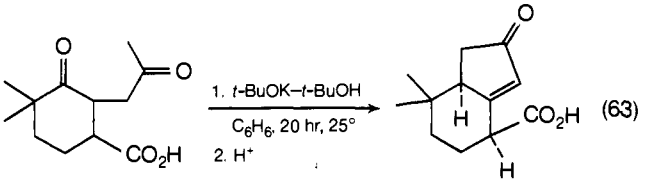
An aldol condensation has also been accomplished in the case of the methyl ketone **101** to give the keto alcohol[78] **102** (eq 62). The condensation does not occur with aluminum *tert*-butoxide or *p*-toluenesulfonic acid.



(62)

101 **102** (~90%)

A third example is that of Miyano and Dorn[79] in which the monocyclic keto acid **103** was converted into the unsaturated bicyclic keto acid **104** (eq 63).

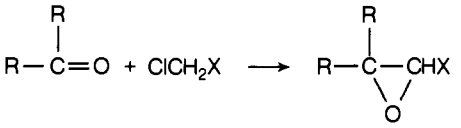


(63)

103 (30 g) **104** (54%) (crude)

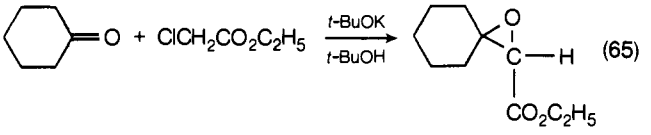
B. Darzens

The Darzens reaction may be represented by



(64)

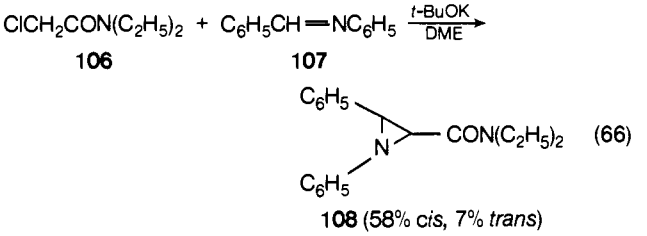
where R = H, alkyl, or aryl and X = COOR, COR, SO_2CH_3, or Ar. Many bases including the *tert*-butoxide have been utilized in the reaction. A typical synthesis[80] of ethyl β,β-pentamethyleneglycidate (**105**) is given in eq 65. Other syntheses using the same base have been described.[81] The *tert*-butoxide gives improved yields in many cases and no imido ester formation occurs as with $NaOC_2H_5$.



(65)

105 (83–95%)

The synthesis of aziridines **108**, from chloroacetic esters **106** and Schiff base **107** by Deyrup and coworkers,[82] may also be regarded as a Darzens reaction (eq 66). However, a carbene mechanism could also be applicable.



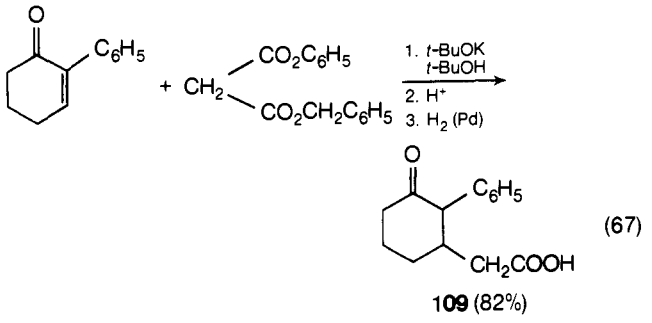
(66)

106 **107** **108** (58% *cis*, 7% *trans*)

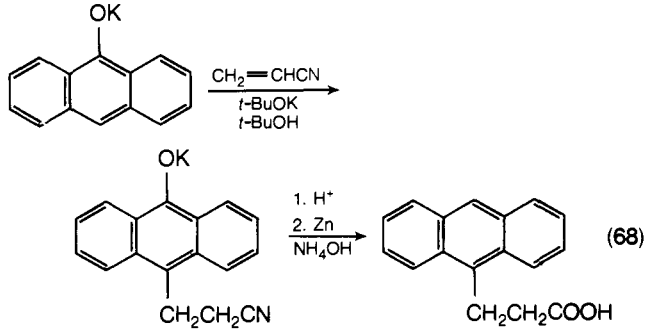
C. Michael

The *tert*-butoxide is one of the many bases employed in the Michael reaction, which has been reviewed.[83] Among the many catalysts tried, so few comparisons have been made that it is difficult to point out any advan-

tage of one over the other. Typical reactions using the *tert*-butoxide are given in the syntheses of *trans*-3-keto-2-phenylcyclohexylacetic acid[84] (**109**) (eq 67) and β-(9-anthranyl)propionic acid[85] (**110**) (eq 68).

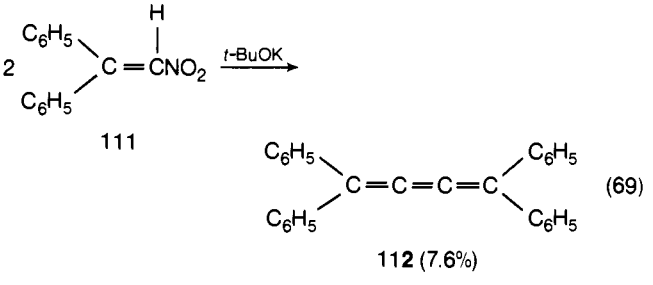


109 (82%) (67)



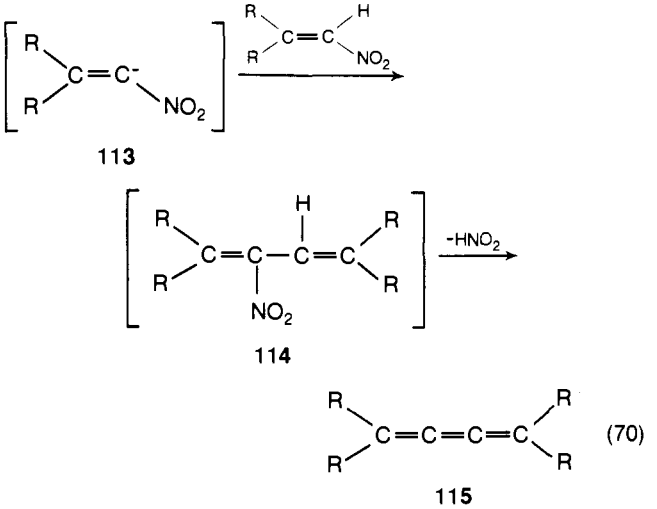
110 (90–95%) (68)

Jones and Broaddus[86] found that 1,1-diphenyl-2-nitroethylene (**111**) when treated with the *tert*-butoxide gives small amounts of tetraphenylbutatriene (**112**) rather than the expected diphenylacetylene (eq 69). It appears



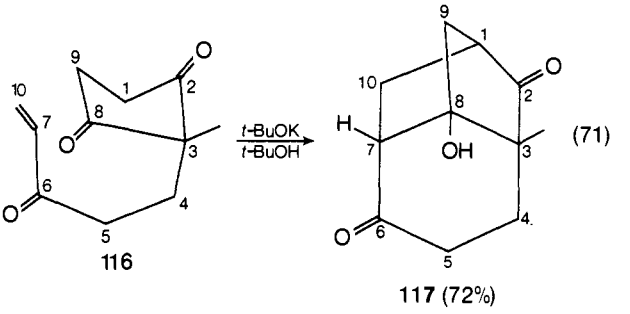
112 (7.6%) (69)

that an unusual Michael addition of the substrate to the carbanion **113** occurs to form a product, **114**, which by elimination leads to the triene **115** (eq 70).



115 (70)

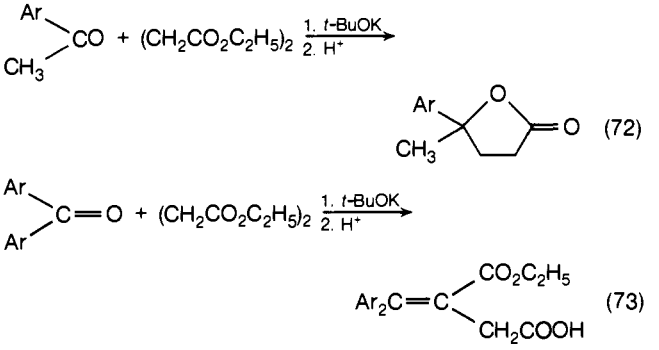
A reaction which appears to be a Michael followed by an aldol condensation is that of Danishefsky and Migdal-of.[87] These investigators converted the enetrione **116** into the homobrendanedione **117** with the *tert*-butoxide (eq 71).



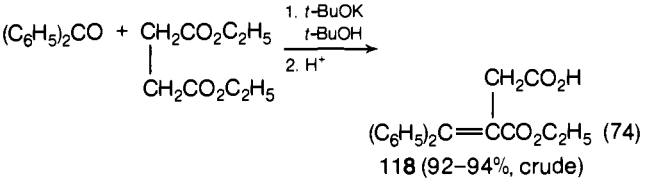
117 (72%) (71)

D. Stobbe

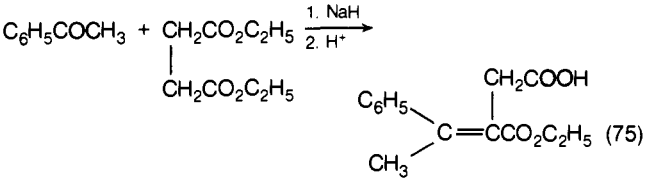
The Stobbe condensation involves largely the reaction of a ketone with succinates or homophthalates to yield lactones (eq 72) or half-esters (eq 73). Originally



$NaOC_2H_5$ was used as the catalyst, but recently the *tert*-butoxide[88] and sodium hydride[89] have been shown to be superior. The effectiveness of the *tert*-butoxide is apparent by the fact that from 1-tetralone and diethyl succinate the half-ester was obtained in 90% yield, while less than a 50% yield was obtained with $NaOC_2H_5$–$(C_2H_5)_2O$.[90] Likewise cyclohexanone gave the half-ester in 84% yield in a 10-min reaction, while the best yields obtained by other methods do not exceed 40%.[90] Typical syntheses with the *tert*-butoxide, β-carbethoxy-γ,γ-diphenylvinylacetic acid (**118**) and with sodium hydride, β-carbethoxy-γ-methyl-γ-phenylvinylacetic acid (**119**) are given in eq 74 and 75, respectively.

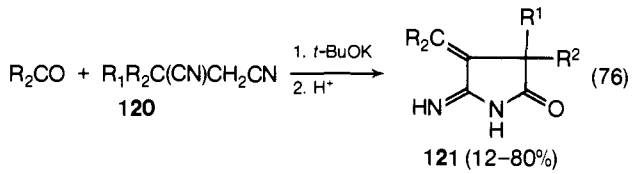


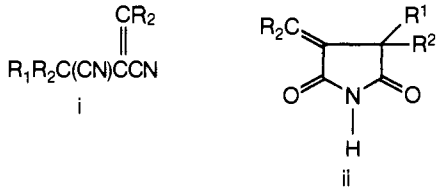
118 (92–94%, crude) (74)



119 (92–93%, crude) (75)

Dinitriles may be substituted for diesters as was shown by Le Ludec and coworkers.[91] These investigators condensed ketones with α,α-dialkylethylenedinitriles (**120**) to obtain iminopyrrolidinones (**121**) (eq 76). It is suggested that the intermediate i cyclizes to form **121**. The *tert*-butoxide proved to be superior to sodium methylate, ethylate, or amide. When R was an alkyl group, the succinimide ii was isolated as a by product.





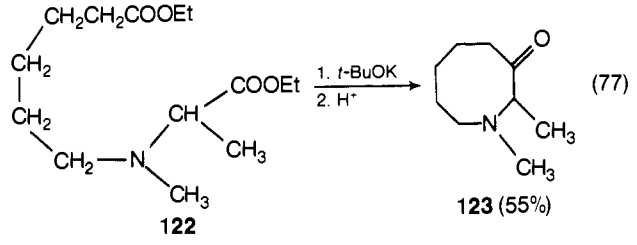
VI. Acylation via Condensation, Deacylation, and Carbonation

The acylations are conducted usually with $NaOC_2H_5$, although the examples cited are those which benefit from the use of the *tert*-butoxide.

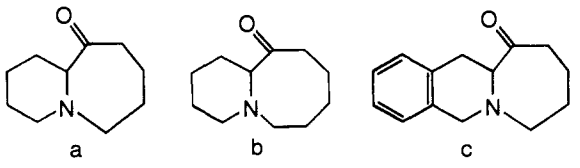
A. Dieckmann. Intramolecular Acylation of Esters and Related Types

1. Amino Diesters

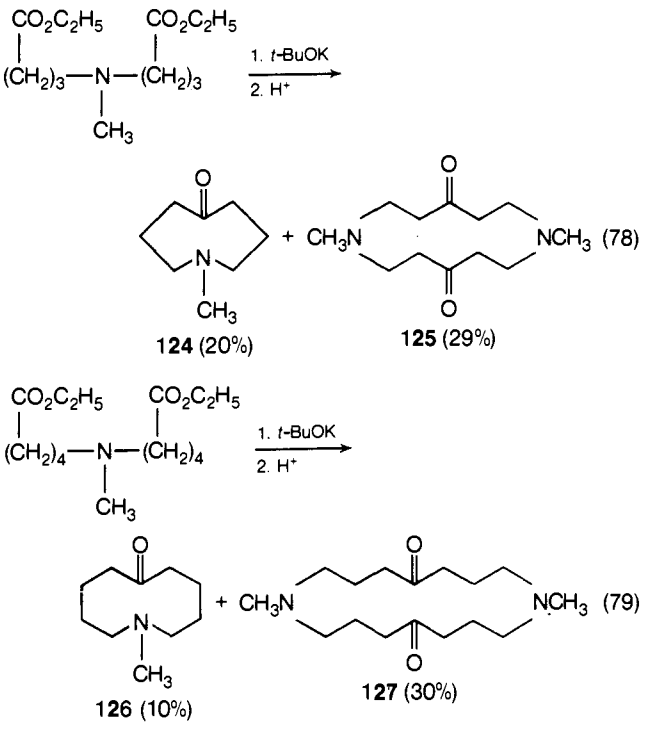
The Dieckmann condensation is a cyclization in which ketones are formed from diesters or related types. It occurs under basic conditions, and it is essential that a hydrogen atom α to at least one of the ester groups be present. One of the earliest examples in which the *tert*-butoxide was used is that of Leonard and Sentz[92] who synthesized 1,2-dimethyl-1-azacyclooctan-3-one (**123**) from α-carbethoxyethyl-ϵ-carbethoxypentylmethylamine (**122**) (eq 77). A high dilution technique was employed with xylene as the solvent, and the alcohol formed was removed with the solvent by azeotropic distillation. Cyclization failed when $NaOC_2H_5$ or NaH was used as the catalyst.



Later Leonard and coworkers[93] employed the same method in synthesizing N-bicyclo types. Although 6-keto-1-azabicyclo[5.4.0]hendecane (a) was obtained in 79% yield from the appropriate diester of piperidine, the analog, 7-keto-1-azabicyclo[6.4.0]dodecane (b), with an eight- rather than a seven-membered ring was produced in 24% yield only. Similarly,[93b] the seven-membered ring type, benzo[*i*]-6-keto-1-azabicyclo[5.4.0]hendecane (c), was obtained in 69% yield from the appropriate diester, while the eight-membered analog by the same method was produced in 42% yield.

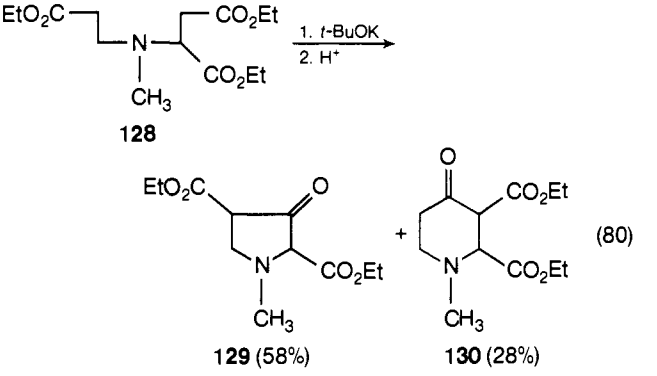


Acyclic amino diesters with the *tert*-butoxide in xylene give two cyclic amino ketones,[94] **124**, **125**, and **126**, **127**, eq 78 and 79, respectively.

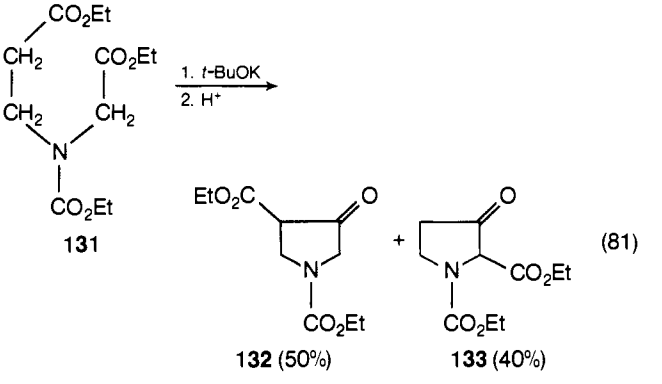


2. Amino Triesters

Under similar, almost nonreversible conditions[95] (*tert*-butoxide in toluene), diethyl *N*-carbethoxyethyl-*N*-methylaspartate (**128**) gives the simpler ketopyrrolidine (**129**) and ketopiperidine[96] (**130**) (eq 80), while NaH in benzene, Na in toluene, or $NaOC_2H_5$ in ethanol led to **130** only.

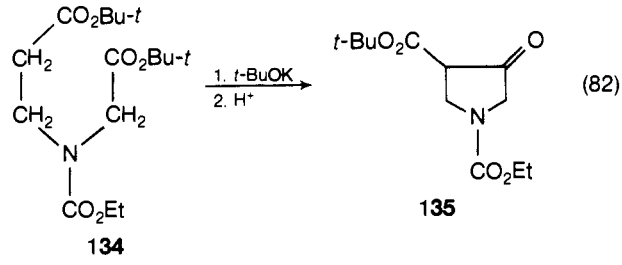


The results with ethyl *N*-ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)glycinate (**131**)[95] are of interest. The *tert*-butoxide in toluene gave the two isomeric pyrrolidones, **132** and **133** (eq 81). The latter, **133**, was not obtained at



all when $NaOC_2H_5$ in ethanol was the reagent, but it was converted completely into **132** with this reagent. Thus the

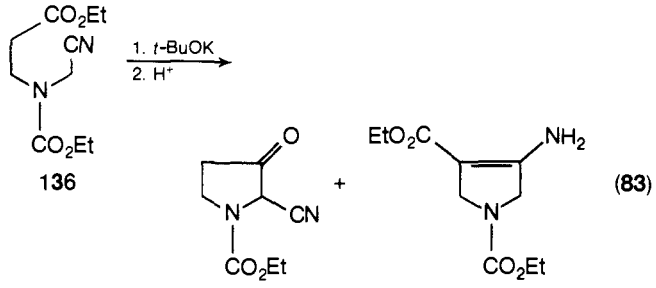
tert-butoxide in toluene may be employed to obtain isomeric forms not available by using $NaOC_2H_5$ in ethanol. On the other hand, the *tert*-butyl ester analog **134** with the *tert*-butoxide in toluene gave none of the 1,2- but only the 1,4-diester (**135**) (eq 82).



134 135 (82)

3. Aminocyano Diesters

If a cyanomethyl group is substituted for the carbethoxymethyl group of **131**, the resulting diester **136** leads to **137** and **138** under essentially nonreversible conditions[95] (eq 83). Sodium ethoxide in ethanol gives 138 only.

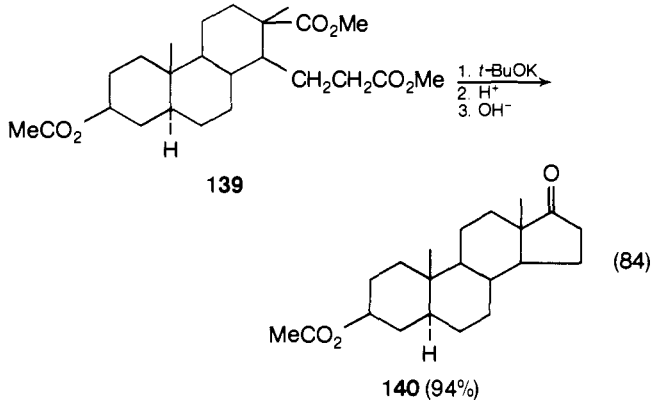


136 137 (55%) + 138 (7%) (83)

4. Diesters

Dicarboxylic esters free from amino groups have been studied by Leonard and coworkers[97] as listed in Table II. Although these yields are not high, they compare favorably with those obtained by the other methods available for preparing large-membered cyclic mono- and diketones.

In the steroid series Johnson and coworkers[98] found the *tert*-butoxide to be effective in the cyclization of the diester of epiandrosterone precursor (**139**) to give the ketone **140** (eq 84). Sodium hydride and the methoxide were ineffective.



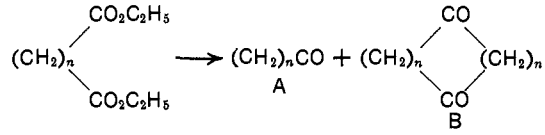
139 140 (94%) (84)

A Dieckmann condensation of a diester of a carboxylic and sulfinic acid (**141**) has been accomplished by Corey and Chaykovsky[99] (eq 85).

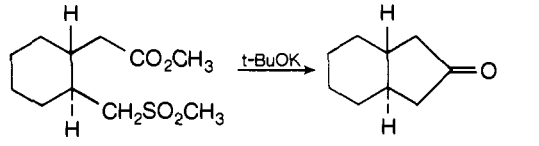
5. Phosphonium Salt of an Ester

To synthesize cyclopentanone, cyclohexanone, and cycloheptanone, House and Babad[100] employed an alternative method of conducting the Dieckmann reaction by proceeding from the phosphonium salt **142** (eq 86). The yields of the intermediate α-ketocycloalkylidenetriphenylphosphoranes varied from 57 to 84%, while the last step gave the cyclic ketones in yields of 90% or better.

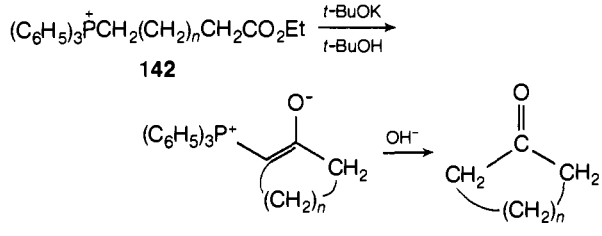
TABLE II. Dieckmann Condensation of Diethyl Esters Using *t*-BuOK in Xylene



n	Product, % A	B
6	47	10
7	15	11
8	0	28
9	0	12
10	0.53	23
11	0.47	16
12	24	19
13	32	2.2
14	48	0.94



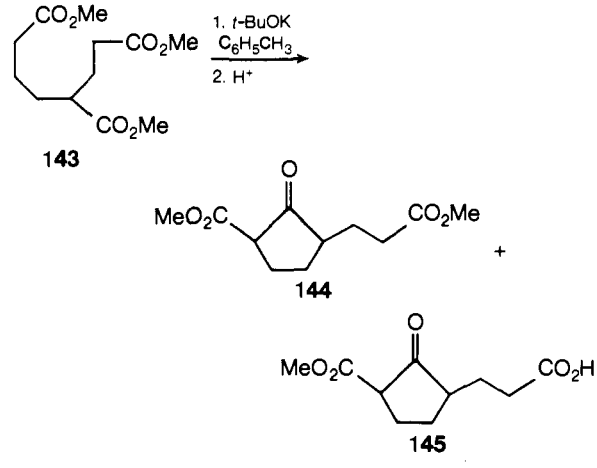
141 (>60%) (85)



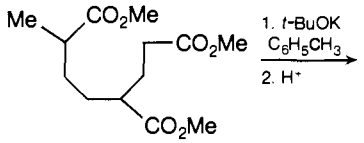
(86)

6. Triesters

Five-membered rings are often formed in preference to six-membered ones, but such is not always the case. For example, trimethyl 1,3,6-hexanetricarboxylate (**143**) with the *tert*-butoxide in toluene followed by acidification gives the five-membered diester **144** and monoester[101] **145** (eq 87), but the 6-methyl derivative **146** under similar conditions leads to the seven-membered di- (**147**) and monoester (**148**) (eq 88).



(87)



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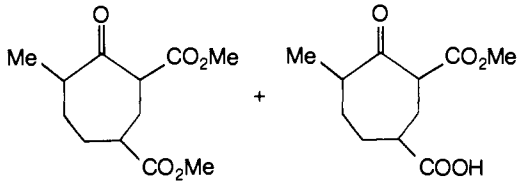
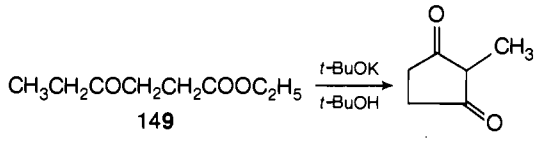


(88)

147 148

7. 4-Ketohexanoate

An example similar to the Dieckmann reaction occurs[102] when methyl 4-ketohexanoate (**149**) is refluxed with the *tert*-butoxide (eq 89).

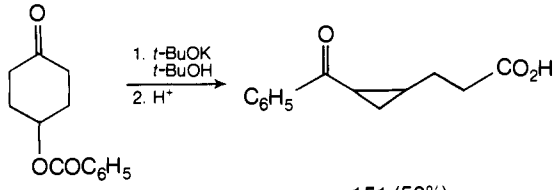


(89)

149 (~50%)

8. 4-Benzoyloxycycloalkanones

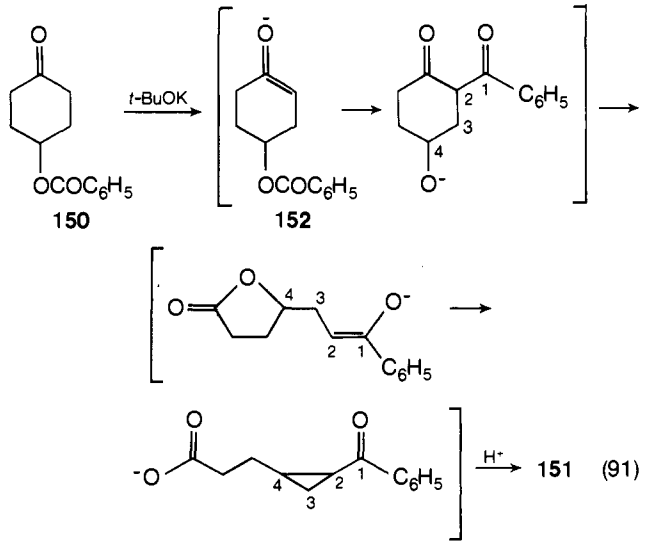
Similar to the Dieckmann as well is Yates and Anderson's discovery[103] that 4-benzoyloxycyclohexanone (**150**) and 4-benzoyloxycycloheptanone are converted into 2-benzoylcyclopropanepropanoic acid (**151**) and 2-benzoylcyclopropanebutyric acid, respectively, by the action of the *tert*-butoxide. The result with **150** is given in



(90)

150 151 (53%)

The steps in the conversion through the enolate anion **152** are indicated in eq 91.

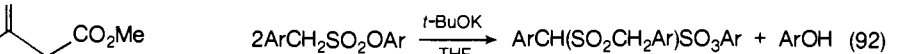


150 152 151 (91)

B. Claisen and Thorpe. Intermolecular Acylation of Esters

1. Aryl Alkanesulfonates

α-Sulfonylation occurs when aryl alkanesulfonates[104] (**153**) are treated with the *tert*-butoxide (eq 92). Tetrahydrofuran is the preferred solvent in the reaction.

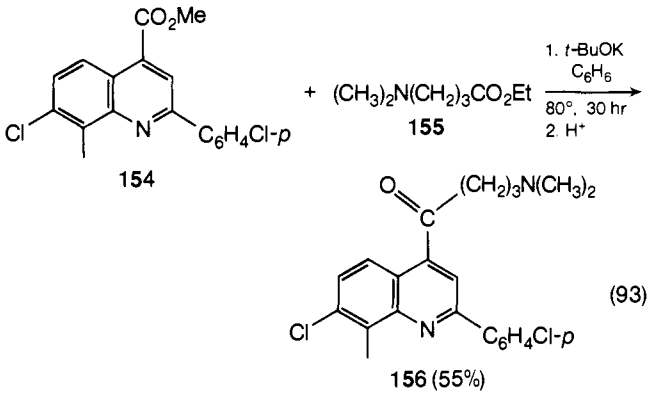


(92)

153 52–69%

2. Methyl Quinolinecarboxylates and Ethyl Aminoalkanecarboxylates

The preparation of some antimalarial intermediates has benefited greatly by the use of the *tert*-butoxide[105] in the so-called mixed Claisen reaction. In one example the methyl quinolinecarboxylate (**154**) was condensed with the ethyl aminoalkanecarboxylate (**155**) to give the quinoline aminoalkyl ketone **156** (eq 93). Dimethyl sulfoxide could not be used as a solvent since its anion condensed in preference to the anion of the amino ester. The yields with $NaOC_2H_5$ were lower or nil.

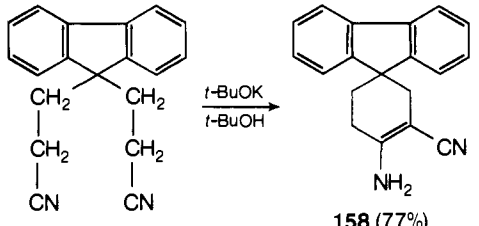


154 155 156 (55%)

(93)

3. Dinitriles

The *tert*-butoxide has been used successfully[106] in the Thorpe condensation in which the dinitrile **157** gives the aminonitrile **158** (eq 94). Attempts at cyclization with $NaOC_2H_5$ or sodium in dioxane failed.

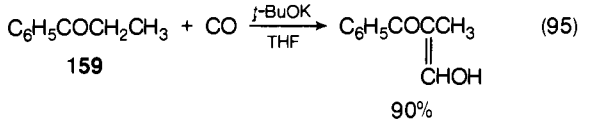


(94)

157 158 (77%)

C. Formylation

The formylation of ketones has been accomplished with carbon monoxide in the presence of the *tert*-butoxide[107] as illustrated with ethyl phenyl ketone (**159**) (eq 95). The yield with $NaOCH_3$ was 72%.

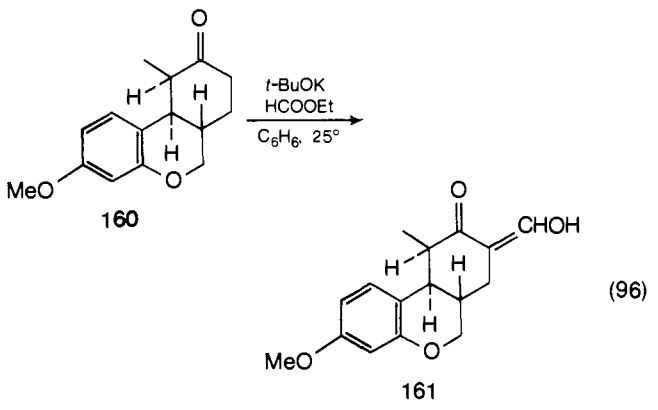


(95)

159 90%

A more recent example is that of Miyano and Dorn[108] in which ethyl formate rather than carbon monoxide was used as the formylating agent. These investigators con-

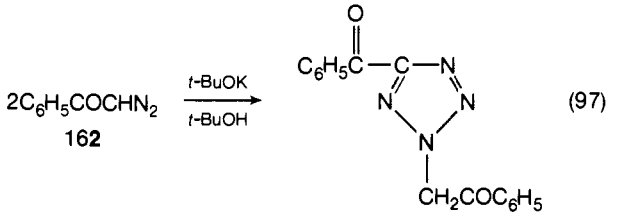
verted the pyran ketone **160** into the hydroxymethylene derivative **161** (eq 96).



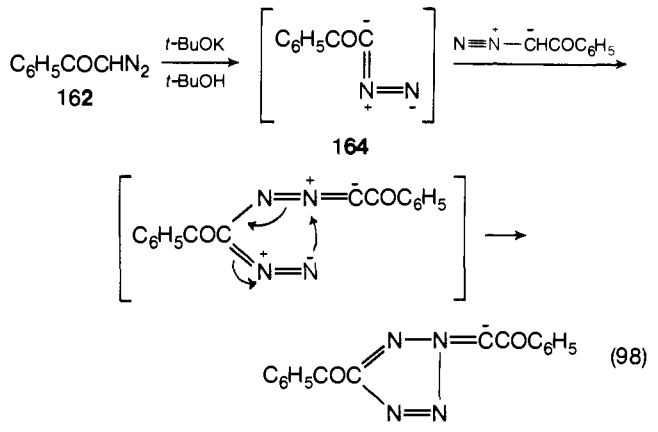
160 161 (96)

D. Tetrazole Formation

A complex reaction, remotely resembling acylation, occurs when 2-diazoacetophenone (**162**) is treated with the *tert*-butoxide. A dimeric product, 5-benzoyl-2-phenacyltetrazole[109] (**163**) (eq 97), forms. The probable mechanism[110] involves the carbanion **164** (eq 98).



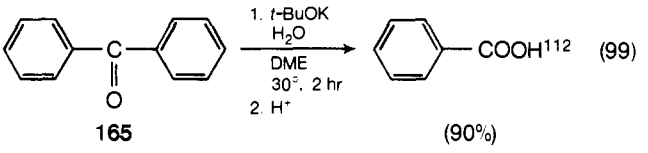
162 163 (69%) (97)



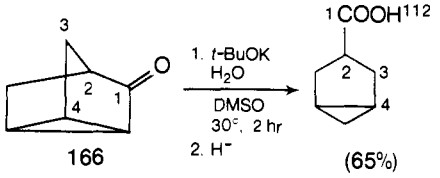
162 164 (98)

E. Deacylation

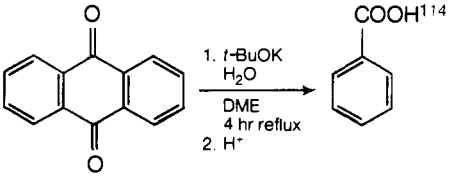
Swan[111] appears to have been the first investigator to split nonenolizable ketones in the presence of the *tert*-butoxide to form carboxylic acids. The reaction has been investigated in more depth by Gassman and coworkers,[112] Davies and Hodge,[113] and Hausigk,[114] all of whom utilized water as a part of the reaction mixture. Gassman recommends a 10:3 ratio of the *tert*-butoxide to water with aprotic solvents such as DMSO, DME, ether, etc. Typical cleavages, such as those of benzophenone (**165**), nortricyclanone (**166**), and anthraquinone (**167**) are given in eq 99, 100, and 101, respectively. The cleavage is similar to the Haller–Bauer reaction, but gives the acid instead of the amide. It is useful in degrading naturally occurring anthraquinones but does not take place if *tert*-butyl alcohol is substituted for water or if other potassium alcoholates, such as the ethoxide or isopropoxide, are used.



165 (90%) (99)

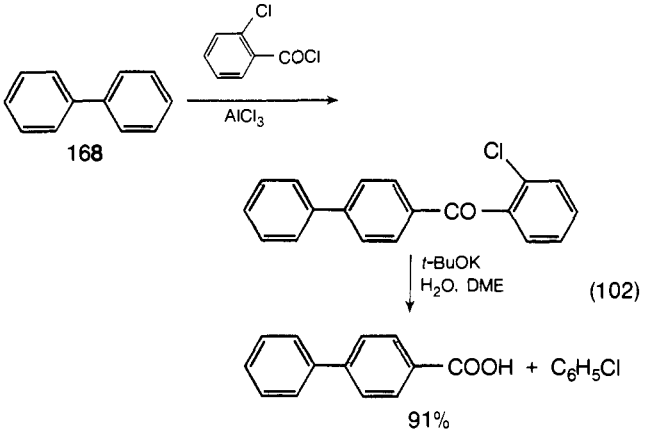


166 (65%) (100)



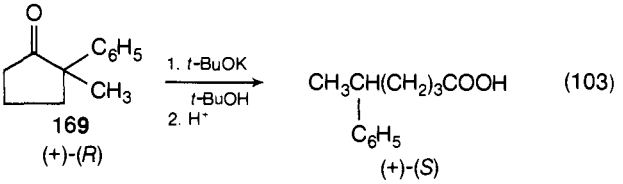
167 (92%) (101)

Davies and coworkers[115] have utilized the deacylation as one step in the introduction of the carboxyl group into aromatic compounds. The complete process is given, as applied to biphenyl (**168**), in eq 102. The use of the *o*-chlorobenzoyl chloride is preferred in the first step since the benzophenone thus formed splits cleanly to give the carboxylic acid desired.



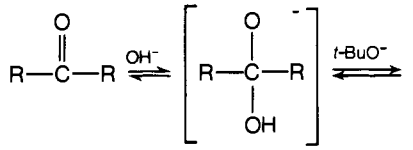
168 91% (102)

Although water is recommended as a part of the reaction mixture, anhydrous conditions sometimes suffice.[116] Such is the case in the cleavage of cyclic ketones, such as 2-phenyl-2-methylcyclopentanone[117] (**169**) (eq 103). For β-keto-α,α-dialkyl esters, House[118] states that the *tert*-butoxide in *tert*-butyl alcohol minimizes cleavage.

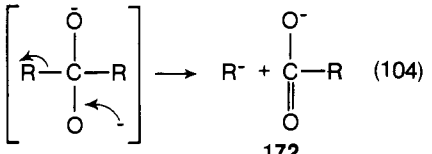


169 (+)-(*R*) (+)-(*S*) (43%, 61% optically pure) (103)

The mechanism of the reaction[112] may be represented by eq 104 in which the hydroxyl ion adds to form the anion **170**, which loses a proton to form the dianion **171** which in turn cleaves to give the anion of the acid **172**.



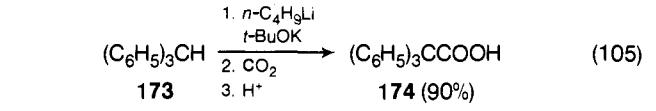
170



171 172 (104)

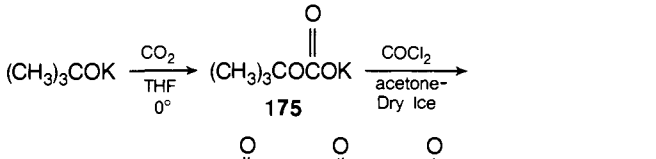
F. Carbonation

It has been stated (section II.B) that the *tert*-butoxide enhances the reactivity of organolithium compounds by breaking down the aggregate into more reactive particles. Thus as shown in eq 105 triphenylmethane (**173**) may be converted into triphenylacetic acid[19] (**174**) in superior yield. Diphenylmethane may be converted into the carboxylic acid in a similar manner. It is interesting to note in this connection (section II.B) that *n*-butyllithium in the presence of the *tert*-butoxide will even metalate benzene.

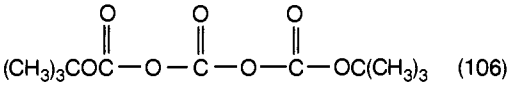


173 **174** (90%) (105)

The use of CO_2 and the *tert*-butoxide has also permitted the formation of a new class of compounds, the tricarbonates.[119] Thus the *tert*-butoxide with CO_2 first forms potassium *tert*-butyl carbonate (**175**) which with phosgene gives di-*tert*-butyl tricarbonate (**176**).



175



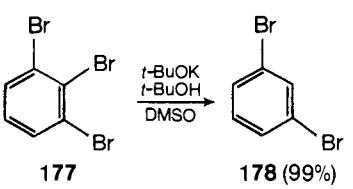
176 (50%) (106)

VII. Elimination

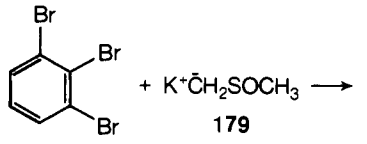
A. Dehalogenation

1. To Dibromobenzene

The dehalogenation of tribromobenzenes occurs in the presence of the *tert*-butoxide.[120] 1,2,3-Tribromobenzene (**177**) gives 1,3-dibromobenzene (**178**) (eq 107). In general, protodehalogenation occurs only at sites ortho to other halogen atoms; in fact, it is most facile for halogens flanked on both sides by halogen. Deiodination occurs more readily than debromination while dechlorination seems not to have been observed. From all the evidence available it appears that bromine (or iodine) is abstracted by the dimsyl anion (**179**) leaving an aryl anion (**180**), eq 108, which then abstracts a proton to form *m*-dibromobenzene.



177 **178** (99%) (107)

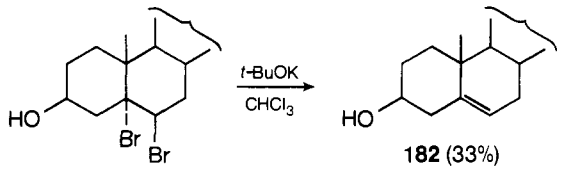


179

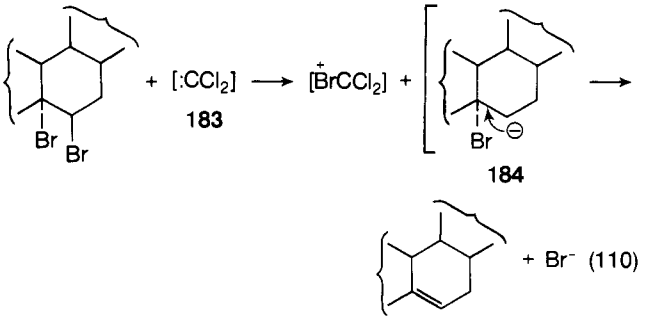
180 (108)

2. To Δ^5-Steroids

The debromination of 5α,6β-dibromo steroids has been accomplished with the *tert*-butoxide[121] as well. In this manner cholesterol (**182**) was obtained from 5α,6β-dibromocholestan-3β-ol (**181**) (eq 109). The reaction is remindful of the manner in which positive bromine was extracted from 1,2,3-tribromobenzene (section VII.A.1). In this case the most likely intermediate is dichlorocarbene (**183**) which removes a positive bromine to form a carbanion (**184**) which by the loss of a negative bromine gives the final product (eq 110). Another possibility is that positive bromine is extracted by the precursor $^-CCl_3$ of the carbene.



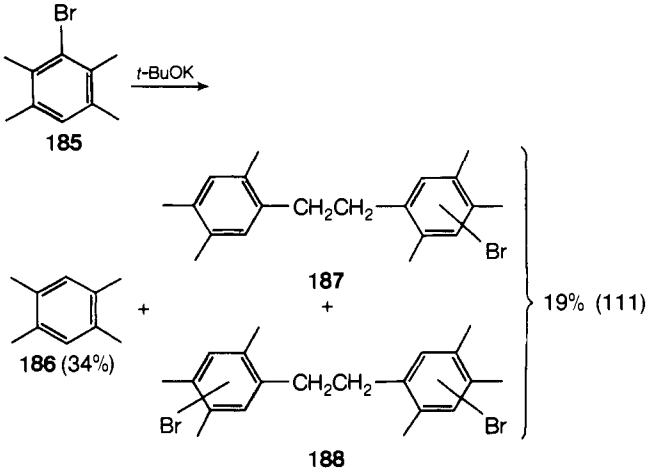
181 **182** (33%) (109)



183 **184** + Br^- (110)

3. To Durene and Mono- and Dibromohexamethylbibenzyls

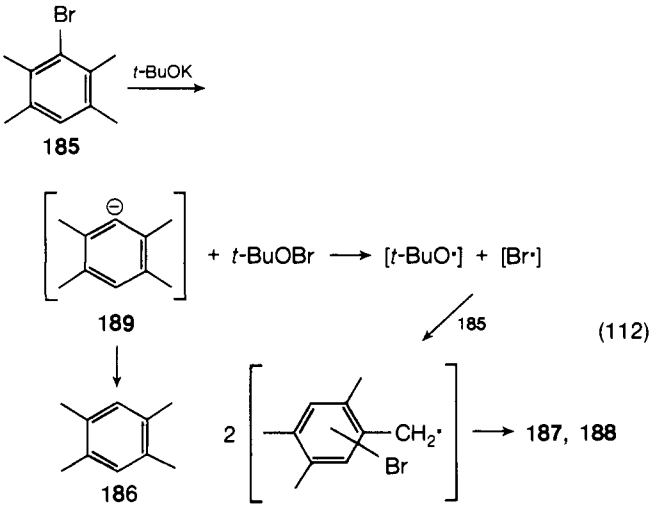
By treating bromodurene (**185**) with the *tert*-butoxide at 225°, Cadogan and coworkers obtained largely durene



185 **186** (34%) **187** **188** 19% (111)

(186) and mono- (187) and dibromohexamethylbibenzyls[122] (188) (eq 111).

A possible mechanism for durene and bibenzyl formation, which involves the carbanion 189, is given in eq 112. Other similar mechanisms may apply. If *t*-BuOBr is indeed formed, it is the first instance of abstraction of positive bromine from a monobromobenzene (see section VII.A.1).



B. Dehydration

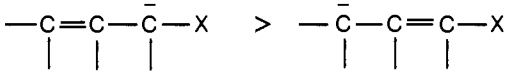
1. To β,γ-Alkenes

Base-catalyzed equilibria for unsaturated salts, esters, and nitriles, and for allyl sulfides, ethers, and amines favor the α,β-alkene.[123] By contrast the alkenes formed from 1-methylsulfinyl- and 1-methylsulfonyl-2-hydroxyundecanes, in the presence of the *tert*-butoxide, are exceptional in that the β,γ-alkene is formed in excess. The dehydration of the 2-hydroxyundecanes (190) to the β,γ-alkene (191) and the α,β-alkene (192) is given by eq 113. When X = $SOCH_3$, the percentage ratio of 191 to

$$C_9H_{19}CHOHCH_2X \xrightarrow[t\text{-BuOH}]{t\text{-BuOK}} \underset{190}{} \quad C_8H_{17}CH{=}CHCH_2X + C_9H_{19}CH{=}CHX \quad (113)$$

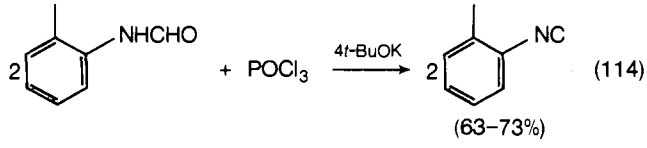
191 192

192 is 96:4, while when X = SO_2CH_3, the ratio is >99:<1, sequences to be expected for the equilibrium in the presence of a strong base.

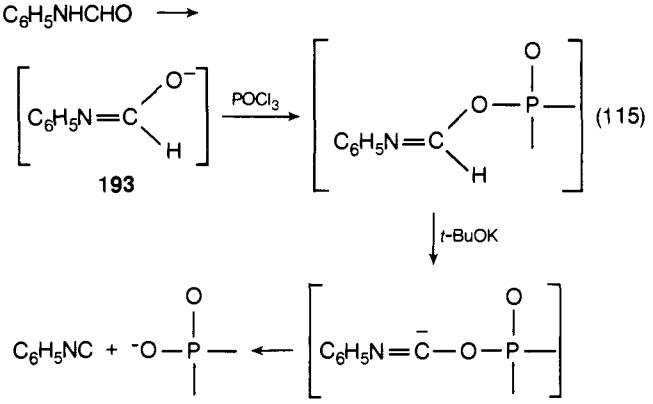


2. To Isocyanides

A general method for the synthesis of aromatic isocyanides involves treatment of the formanilide with phosphorus oxychloride and the *tert*-butoxide[124] (eq 114).

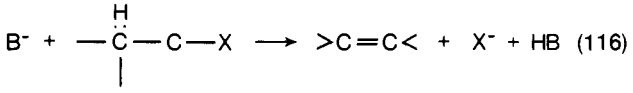


Yields for a series of formanilides vary from 25 to 88%. The *tert*-butoxide is superior to pyridine which is preferred in the aliphatic series; it is also preferable to sodium *tert*-butoxide and other bases. In the reaction an α-elimination probably occurs, leading first to the anion 193 and finally to the isocyanide (eq 115).



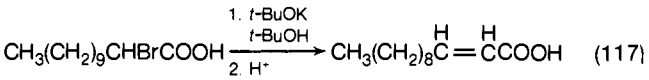
C. Dehydrohalogenation to Unsaturated Compounds, Diaziridinones, Ylides, and Carbenes

The process may be represented by eq 116. The elimination covers E2 and E1cB types and it soon becomes apparent that the size of the aggregate and the basicity of the *tert*-butoxide are important in determining the products formed.



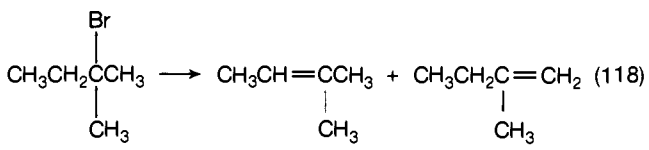
1. Alkenes and Dialkenes

Cason and coworkers[125] in investigating methods for preparing α,β-unsaturated carboxylic acids from α-halocarboxylic acids called attention to the superiority of the *tert*-butoxide in *tert*-butyl alcohol over KOH in methanol. These investigators obtained 2.75 g of pure 2-dodecenoic acid from 10 g of 2-bromododecanoic acid (eq 117). Po-



tassium hydroxide in methanol, ethanol, or propanol gave lower yields. The same method has been employed for the preparation of *trans*-2-dodecenoic and 2-methylenedodecanoic acids.[126]

Brown and Moritani[127] found that when elimination in alkyl halides with KOC_2H_5 gives largely the nonterminal olefin (Saytzeff product), the terminal olefin (Hofmann product) may be produced in excess by using the *tert*-butoxide or another alkoxide of greater steric requirements. Thus 2-bromo-2-methylbutane gives the alkenes shown in eq 118. With KOC_2H_5 the percentage of 1-olefin



is 29, with $KOC(CH_3)_3$ it is 72, with $KOC(CH_3)_2(C_2H_5)$ it is 78, and with $KOC(C_2H_5)_3$ it is 89. In a later study[128] with 2-butyl and *tert*-amyl halides and the *tert*-butoxide in *tert*-butyl alcohol, the amount of 1-olefin was almost always in excess of the 2-olefin and the ratio of 1- to 2- increased in the order Cl > Br > I. Bartsch and Bunnett[129] continued the study with 2-haloalkanes using the *tert*-butoxide in *tert*-butyl alcohol and in DMSO, and $NaOC_2H_5$ in ·methyl alcohol. With the *tert*-butoxide in *tert*-butyl alcohol

TABLE III. Percentages of Alkenes from 2-Bromoheptane at 30°

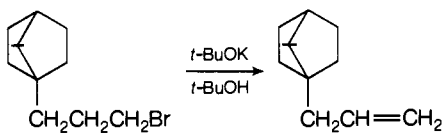
Base mixture	1-Alkene	*trans*-2-Alkene	*cis*-2-Alkene
t-BuOK–*t*-BuOH	87.5	7.2	5.3
t-BuOK–DMSO	49.0	42.3	8.7
$NaOCH_3$–CH_3OH	19.7	64.4	15.9

Hofmann orientation predominated with all substrates. With the *tert*-butoxide in DMSO some isomerization resulted at high temperatures and the reaction was essentially complete on mixing. Thus to obtain the highest percentage of 1-alkene, the *tert*-butoxide in *tert*-butyl alcohol is preferred as will be explained later. On the other hand, $NaOCH_3$ in methanol yields the highest return of 2-alkenes. A typical comparison follows in Table III.

Bartsch and coworkers[130] continued the study of elimination from 2-butyl chloride, bromide, and iodide with a variety of bases in alcoholic dipolar aprotic and mixed solvents. The highest yields (~80%) of 1-butene were obtained from 2-butyl chloride and potassium triethylmethoxide in triethylcarbinol. Potassium *tert*-butoxide in *tert*-butyl alcohol gave 67% of the 1-isomer. The highest yield of *trans*-2-butene (78%, *trans*–*cis* ratio ~4:1) was obtained from 2-butyl iodide and lithium chloride in DMF. The maximum yield from the *tert*-butoxide, by using 2-butyl bromide and dimethylacetamide, was 57% (trans-cis ratio 3.5:1).

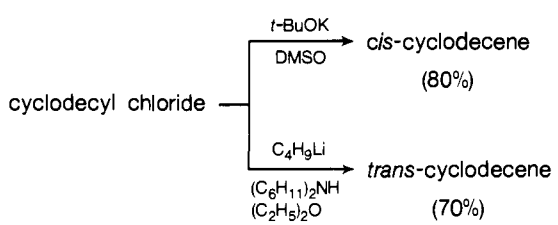
Arnold and coworkers[131] showed that in the dehydrohalogenation of certain higher alkyl halides with the *tert*-butoxide in *tert*-butyl alcohol superior yields were obtained (eq 119 and 120).

$$C_{18}H_{37}Br \xrightarrow[t\text{-BuOH}]{t\text{-BuOK}} C_{16}H_{33}CH{=}CH_2 \quad (85\%) \qquad (119)$$



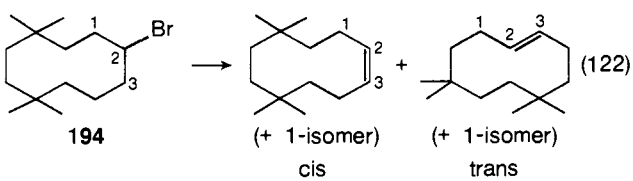
(100%) (120)

The condition of the *tert*-butoxide, *i.e.*, whether it is an aggregate or a more nearly monomeric form, has some influence on the yields of cis *vs.* trans olefin from an elimination reaction. Traynham[132] was the first to demonstrate that such differences are to be expected (eq 121),



(121)

but it remained for a group of Czechoslovakian investigators[133] to show that the difference in yield of cis or trans forms was caused by the variation in the size of the aggregate of the *tert*-butoxide. The percentages obtained from 2-bromo-5,5,8,8-tetramethylcyclooctane (**194**) (eq 122) are given in Table IV. Each of two components of



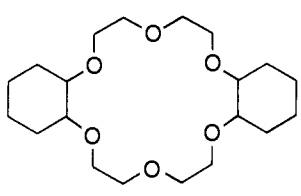
(122)

TABLE IV. Percentages of Trans and Cis Isomers from 194 by Treatment with *t*-BuOK in Various Solvents

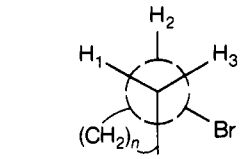
Solvent	% *trans*[a]	% *cis*[a]
C_6H_6	83	1.5
C_6H_6 + **195**	9	76
DMF	7	72
DMF + **195**	4	80

[a] Total of trans or cis 1- and 2-olefins.

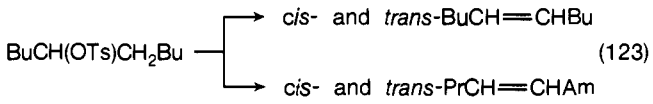
the reaction mixture, DMF (an aprotic solvent like DMSO) and dicyclohexyl-18-crown-6-ether (**195**), increases the amount of the *cis*-cycloalkene. Both act to reduce the size of the aggregate by complexing with the potassium ion. The reason the smaller *tert*-butoxide complex in DMF or with **195** should give more of the cis form is not clear as yet,[134] but no doubt it is related to the accessibilities of the β hydrogens, H_1 and H_3, in the various conformations, one of which is shown below.



195



On the other hand, elimination from open-chain compounds leads to trends which are opposite to those for elimination from cyclic compounds; *i.e.*, the smaller aggregates of *tert*-butoxide favor the formation of the trans alkene. For instance, the Czechoslovakian investigators[135] have examined the dehydrotosylation of an open-chain tosylate (eq 123). The results with the *tert*-butoxide alone and with the crown ether **195** in various solvents are given in Table V,



(123)

Bartsch and coworkers[136] have confirmed the work of the Czechoslovakians in observing the dehydrotosylation of *sec*-butyl tosylate. With *t*-BuOK–*t*-BuOH the 2-butene trans/cis ratio was 0.4, while when the crown ether **195** was substituted for the alcohol the value became 1.88.

It is to be noted in Table V that the amount of trans isomer is increased in C_6H_6 and *t*-BuOH as the size of the *t*-BuOK aggregate is decreased, results opposite to those in the cyclic series with **194**. In other words the trans isomer is favored with the small *tert*-butoxide aggregate from conformation **196a** while the cis is slightly favored from **196b**. The control of the elimination products by the size or shape of the aggregate is a phenomenon of great importance. More clearcut results can be

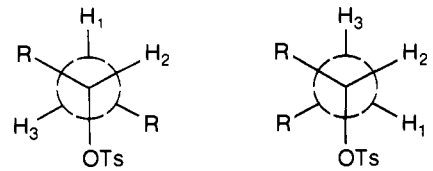
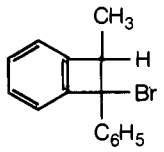


TABLE V. Ratios of Trans to Cis Olefins (*trans*-4- and 5-Decene to *cis* 4- and 5-Decene) from 5-Decyl Tosylate and Base with Various Solvents

Base	C_6H_6	*t*-BuOH	DMF
t-BuOK	0.85	0.41	3.16
t-BuOK + **195**	2.12	2.54	3.16

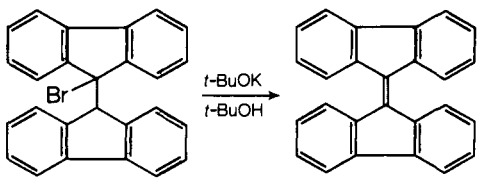
expected once the nature of the transition complex is determined.[137]

Despite the manipulative capability of the *tert*-butoxide in dehydrohalogenation, it is not always a successful reagent. To cite one case, 2-bromo-1-methyl-2-phenylbenzocyclobutene (**197**) gives only the *tert*-butyl ether.[138]



197

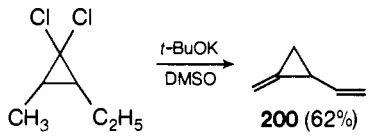
On the other hand, with the bulky molecule 9-bromo-9,9'-bifluorenyl (**198**) the alkene is obtained quantitatively.[139]



(124)

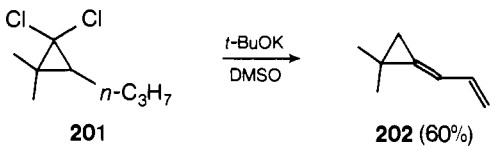
198

The dehydrochlorination of alkylated dichlorocyclopropanes with the *tert*-butoxide was investigated by Shields and coworkers.[140] These investigators found that the 1,1-dichloro-2-ethyl-3-methylcyclopropane (**199**) gave vinylmethylenecyclopropane (**200**), while 1,1-dichloro-2,2-dimethyl-3-propylcyclopropane (**201**) gave 2,2-dimethylallylidenecyclopropane (**202**), eq 125 and 126, respectively. On heating, both of these products rearrange to cyclopentenes.



(125)

199 **200** (62%)

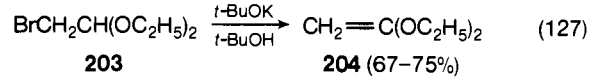


(126)

201 **202** (60%)

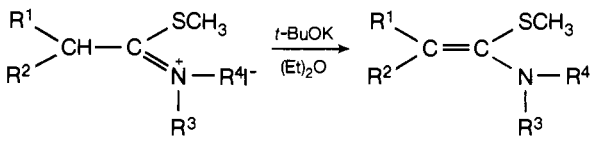
2. *Ketene Acetals, Ketene S,N-Acetals, and Vinyl Orthoformate*

As has already been shown in the synthesis of α,β-unsaturated acids (section VII.C.1), substituted halides may be dehydrohalogenated to the corresponding alkenes. Thus diethyl β-bromoacetal (**203**) with the *tert*-butoxide gives diethylketene acetal[141] (**204**) (eq 127). Similarly ketene *S,N*-acetals (**206**) may be produced from the *S*-methylthioimidium iodides[142] (**205**) (eq 128).



(127)

203 **204** (67–75%)



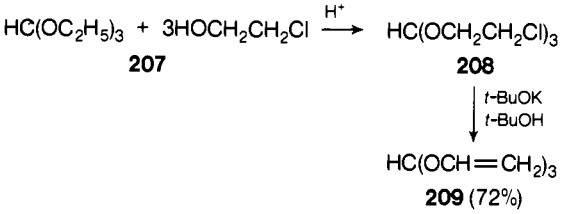
205 **206**

(58–81%; 80–90% purity)

R^1, R^2 = H, alkyl, or $(CH_2)_2$ or $(CH_2)_3$ (for both) (128)

R^3, R^4 = CH_3, C_6H_5, or CH_2CH_2O or $(CH_2)_2$ (for both)

Vinyl orthoformate (**209**) is available from β-trichloroethyl orthoformate (**208**) produced from ethyl orthoformate[143] (**207**).

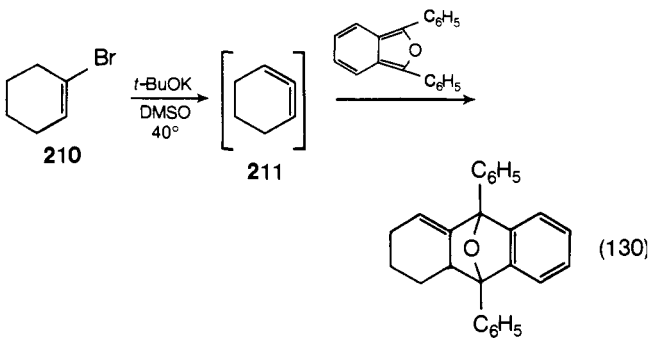


(129)

207 **208** **209** (72%)

3. *Cyclenes, Cyclodienes, and Cyclotetraenes*

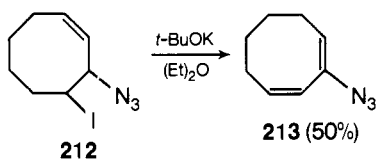
The formation of *cis*- and *trans*-cyclodecene from cyclodecyl chloride has already been given (section VII.C.1). 1,2-Cyclohexadiene (**211**) was obtained by Wittig and Fritze[144] by treatment of 1-bromo-1-cyclohexene (**210**) with the *tert*-butoxide (eq 130). Since the diene (**211**) was unstable it was trapped with 1,3-diphenylbenzo[c]furan to give the adduct indicated.



(130)

210 **211** (30%)

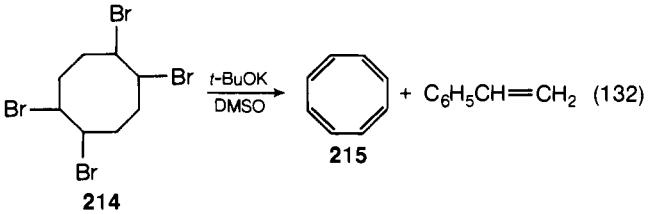
2-Azido-1,3-cyclooctadiene (**213**) has been obtained by Hassner and coworkers[145] from 3-azido-4-iodocyclooctene (**212**) (eq 131). The substrate is readily available from cyclooctadiene and iodine azide.



(131)

212 **213** (50%)

Gardner and coworkers[146] dehydrohalogenated 1,2,5,6-tetrabromocyclooctane (**214**) to obtain cyclooctatetraene (**215**) (eq 132). The base mixture employed was preferred over CH_3SOCH_2Na in DMSO.



(132)

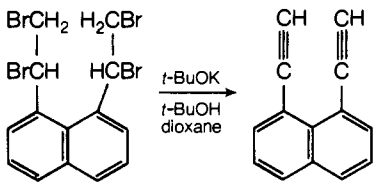
214 **215**

4. Aliphatic, Alicyclic, and Aromatic Ynes, and Alkenynes

Hexyne-1 (**217**) was produced by Cherkasova and Gurevich[147] by the dehydrohalogenation of 1,2-dibromohexane (**216**) (eq 133). With KOH the yield was 43%.

$$\underset{\textbf{216}}{CH_3(CH_2)_3CHBrCH_2Br} \xrightarrow[C_6H_{11}OH]{t\text{-BuOK}} \underset{\textbf{217 (60\%)}}{CH_3(CH_2)_3C{\equiv}CH} \quad (133)$$

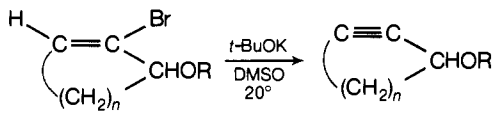
1,8-Diethynylnaphthalene (**219**) results on the dehydrobromination of 1,8-bis(1,2-dibromoethyl)naphthalene[148] (**218**) (eq 134). Sodamide (excess) in liquid ammonia gave a 61% yield of 1,8-divinylnaphthalene.



(134)

218 **219** (79%)

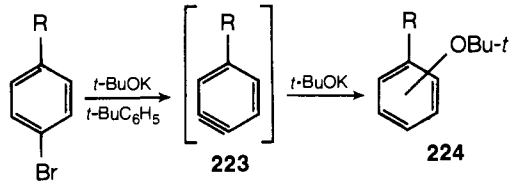
Cyclooctynes and cyclononynes (**221**) of the type shown in eq 135 have been produced by Reese and Shaw[149] from the corresponding bromocyclene (**220**). The reaction occurs in a few minutes with yields given in Table VI. The formation of medium-sized unsubstituted cycloalkynes by the *tert*-butoxide has been discussed recently.[150]



(135)

220 **221**

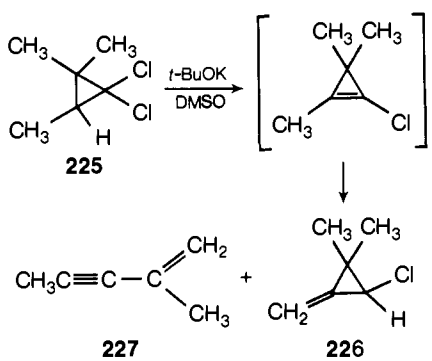
Arynes (**223**) have been produced by Cram (section III.G.1) and by Cadogan and coworkers[151] from aryl halides (**222**) and the *tert*-butoxide alone or more conveniently in *tert*-butylbenzene (eq 136). The presence of the unstable aryne was shown by its conversion into the *tert*-butyl ether (**224**) (largely meta and para) and by the formation of triptycenes with anthracene.



(136)

222 **223** **224**

It has been shown (section VII.C.1) that certain alkyl-substituted dichlorocyclopropanes give dialkenes in which the cyclopropane ring is retained. In some cases, however, alkenynes are produced as well. For example, 1,1-dichloro-2,2,3-trimethylcyclopropane (**225**) when



(137)

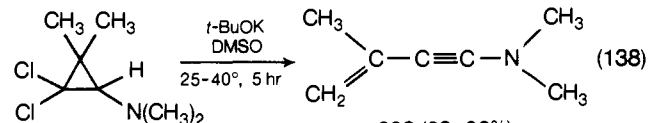
225 **227** **226**

TABLE VI. Yields of Cyclyne Ethers from Bromocyclene Ethers

n	R	Yield, %
5	CH_3	74
5		High
6	CH_3	70
6	H	60

subjected to the *tert*-butoxide gives largely the methylenecyclopropane **226** and the alkenyne[152] **227** (eq 137).

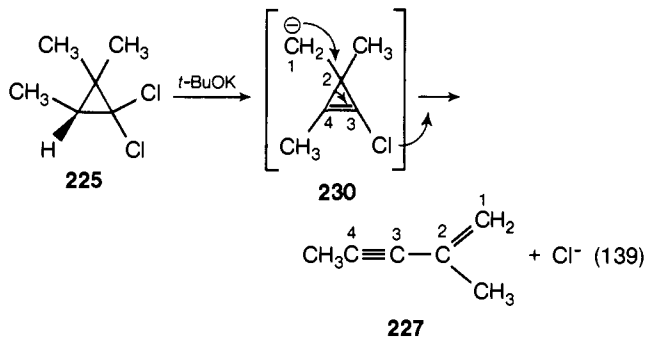
Similarly (2,2-dichloro-3,3-dimethylcyclopropyl)dimethylamine (**228**) gives the alkenyne[153] **229** (eq 138). It is



(138)

228 **229** (20–30%)

suggested that these dehydrohalogenations may proceed *via* the cyclopropene carbanion **230** (eq 139). It should be mentioned, however, that attempts to trap the cyclopropene intermediate were unsuccessful.

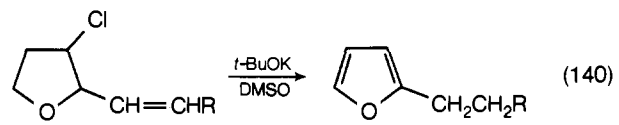


(139)

225 **230** **227**

5. Alkylfurans and Alkylthiophenes

Gouesnard and Martin[154] subjected 2-alkenyl-3-chlorotetrahydrofurans (**231**) to the action of the *tert*-butoxide and obtained 2-alkylfurans (**232**) (eq 140). In a similar manner an alkylthiophene was obtained in 18–20% yield from 2-alkenyl-3-chlorotetrahydrothiophene.



(140)

231 **232** (25–30%)

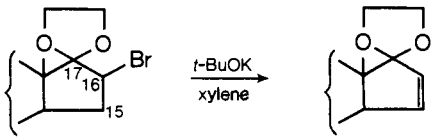
6. Δ Steroids

In comparing the effect of the *tert*-butoxide on certain halides and tosylates, Wood and Chang[155] confirmed Arnold's study[131] which showed that halides, as 24-cholanyl chloride (**233**), give essentially alkenes while tosylates, as 24-cholanyl tosylate (**234**), give largely substitution products, eq 141 and 142, respectively.

$$\underset{\textbf{233}}{\text{24-cholanyl chloride}} \xrightarrow[DMSO]{t\text{-BuOK}} \underset{79\%}{\text{23-ene}} + \underset{21\%}{\text{ether}} \quad (141)$$

$$\underset{\textbf{234}}{\text{24-cholanyl tosylate}} \xrightarrow[DMSO]{t\text{-BuOK}} \underset{21\%}{\text{23-ene}} + \underset{78\%}{\text{ether}} \quad (142)$$

To dehydrohalogenate 16-bromo-17-keto steroids, Johnson and Johns[156] found it necessary to protect the keto group as the ketal and then reflux with the *tert*-butoxide. Thus the bromoketal **235** yielded the 15-ene **236** (eq 143). Mild acid hydrolysis gave the 15,16-dehydro steroid.

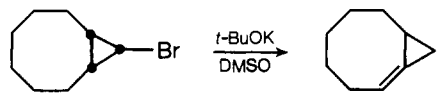


(143)

235 **236** (72%)

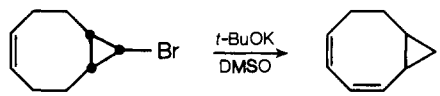
7. Unsaturated Bicyclic Hydrocarbons, 6-Methyl-2-norbornanone, and 3-Chlorotricyclo[3.3.0.$0^{2,6}$]oct-7-ene

Unsaturated bicyclic hydrocarbons have been synthesized by Gardner and coworkers[157] by subjecting the appropriate bromocyclopropanes to the *tert*-butoxide. In this manner *cis*-9-bromobicyclo[6.1.0]nonane (**237**) gave largely bicyclo[6.1.0]non-1-ene (**238**) (eq 144), *cis*-9-bromobicyclo[6.1.0]non-4-ene (**239**) gave the 2,4-diene (**240**) (eq 145), and 9,9-dibromobicyclo[6.1.0]non-4-ene (**241**) gave largely methylcyclooctatetraene (**242**) and bicyclo[4.3.0]nona-2,4,7-triene (**243**) (eq 146). The intermediates here doubtless contain a double bond in the three-membered ring, but migration usually occurs to a position of greater stability in the larger ring.



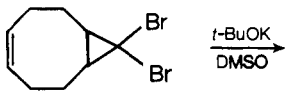
(144)

237 **238** (76%)

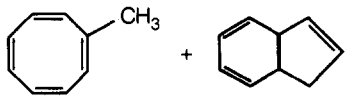


(145)

239 **240** (57–70%)



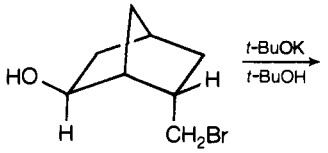
241



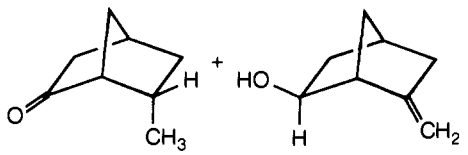
(146)

242 (53%) **243** (23%)

Gwynn and Skillern[158] dehydrohalogenated *endo*-6-bromomethyl-*exo*-2-norbornanol (**244**) with the *tert*-butoxide to obtain 6-*endo*-methyl-2-norbornanone (**245**) and 6-methylene-2-*exo*-norbornanol (**246**) in a 3:1 ratio, respectively (eq 147). In this transformation it appears that the ketone results through a 1,4-hydride shift.



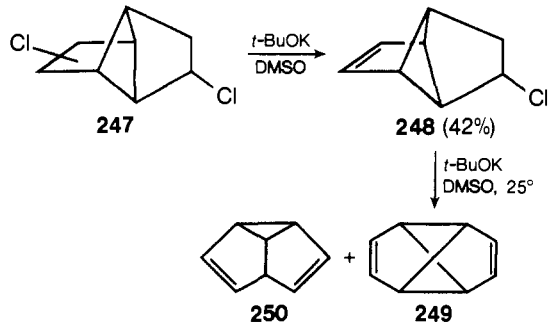
244



(147)

245 **246**

The dehydrochlorination of dichlorotricyclo[3.3.0.$0^{2,6}$]-octane (**247**) with the *tert*-butoxide was accomplished by Meinwald and Tsuruta[159] (eq 148). The first product, 3-chlorotricyclo[3.3.0.$0^{2,6}$]oct-7-ene (**248**), was converted into tricyclo[3.3.0.$0^{2,6}$]octa-3,7-diene (**249**) and semibullvalene (**250**). With time at room temperature **249** changes into **250**. These two highly strained ring systems have recently become of interest.

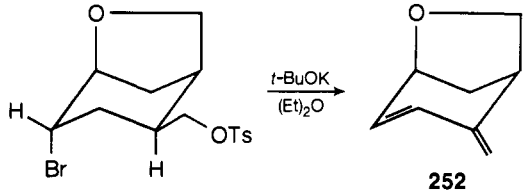


(148)

247 **248** (42%) **250** **249**

8. Methylene Oxabicyclo[3.2.1]octene

A dehydrobromination and a dehydrotosylation occur when the 4-bromo-6-oxabicyclo[3.2.1]methyl tosylate (**251**) is subjected to the action of the *tert*-butoxide;[160] the product is methylene oxabicyclo[3.2.1]octene (**252**) (eq 149).

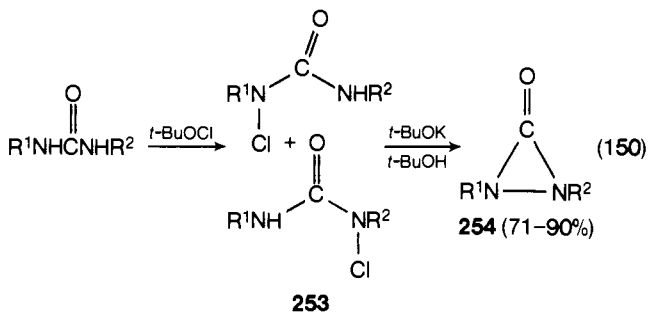


(149)

251 **252**

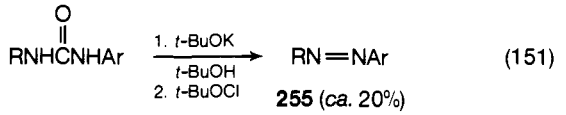
9. Diaziridinones

Diaziridinones (**254**) have been synthesized from *N*-chloroureas (**253**) and the *tert*-butoxide by Greene and coworkers,[161] presumably in a Hofmann-like rearrangement (eq 150). By substituting potassium for the *tert*-butoxide in the case of 1,3-di-*tert*-butylurea, a lower yield was obtained (48% rather than 90%). The diaziridinones may also be obtained from the carbazyl chloride and the *tert*-butoxide,[161] but the yields are less satisfactory. Some of the ureas may yield azo compounds (**255**) presumably as represented in eq 151.



(150)

253 **254** (71–90%)



(151)

255 (*ca.* 20%)

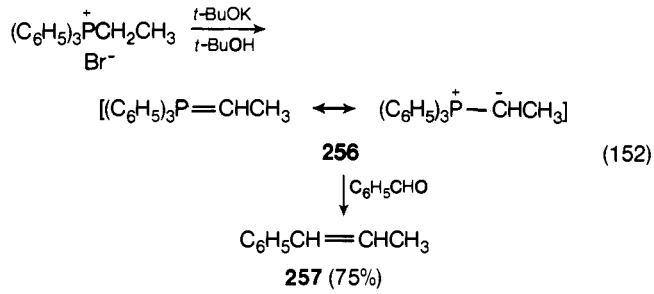
10. Ylides

The *tert*-butoxide appears to have been used in two methods of dehydrohalogenation, both of which yield yl-

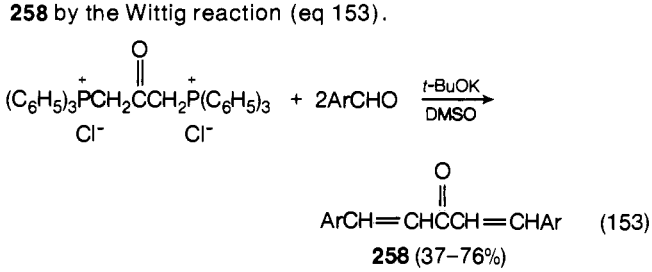
ides.[162] Occasionally other acids are eliminated as is shown in eq 155, but the hydrogen halide removal appears to be the most common.

a. Elimination of HX from a Phosphonium or Sulfonium Halide

The first of these is illustrated in the Wittig reaction in which the ylide **256** is an intermediate in the formation of alkenes[163] **257** (eq 152). In the absence of the *tert*-butoxide the yield of alkene is 0–5%. Similarly *t*-BuOK–DMSO[164] has been shown to be preferable to $NaOC_2H_5$–C_2H_5OH or butyllithium in the synthesis of divinyl ketones **258** by the Wittig reaction (eq 153).

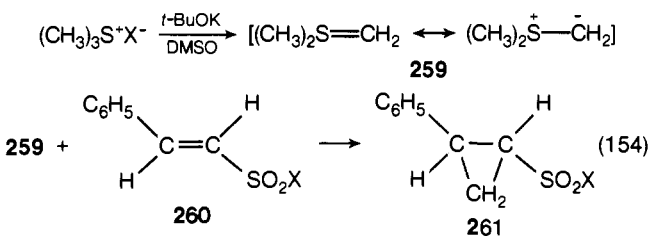


(152)



(153)

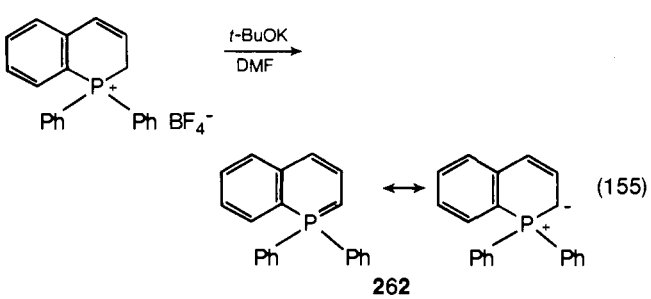
Truce and Goralski[165] carried out the elimination of the sulfonium halide. These investigators prepared *trans*-cyclopropanesulfonic acid esters and amides (**261**) by the Michael addition of dimethylsulfonium methylide (**259**) to *trans*-2-phenylethenesulfonic acid esters or amides (**260**) (eq 154).



(154)

If X = OAr, yield = 60–79% If $X = N(C_6H_5)_2$, yield = 88%

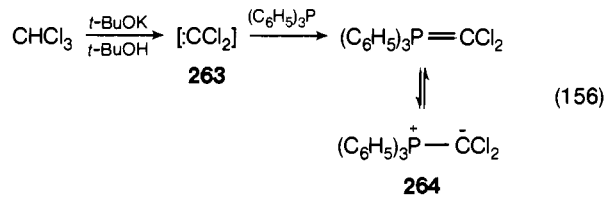
In preparing other ylides the loss of the elements of an acid is quite variable depending on the acidity of the proton removed. They may be removed by bases such as butyllithium employed for the preparation of methylenetriphenylphosphorane or aqueous sodium hydroxide utilized in the preparation of carbomethoxymethylenephosphorane.[162] An example in which an acid other than the hydrogen halide has been eliminated is that of Märkl[166] (eq 155). Here tetrafluoroboric acid is removed to give a cyclic methylenephosphorane (**262**) which is easily oxidized by air.



(155)

b. Elimination to Form a Carbene Which Reacts with a Triphenylphosphine to Form the Ylide

Speziale and Ratts[167] synthesized phosphinedichloromethylenes (**264**) by the action of the *tert*-butoxide on the appropriate halide with triphenylphosphine serving as a trap for the carbene (**263**) (eq 156). It is desirable to use the product immediately; with carbonyl compounds it produces dichloroethylenes with yields varying from 29 to 83%.



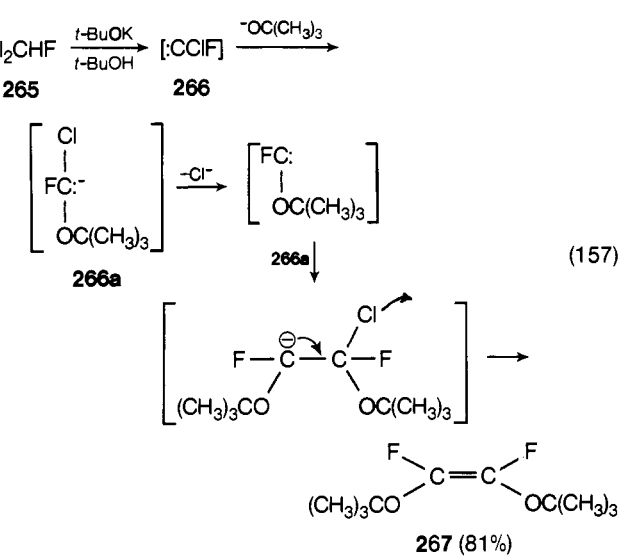
(156)

11. Carbenes

Carbenes[168] are now recognized as common intermediates in many organic reactions. They are readily prepared from certain halides by the action of a base such as the *tert*-butoxide.[169] In this section several illustrations are given, in which carbenes, prepared by the *tert*-butoxide, are of value in organic syntheses. Other cases in which carbenes are an intermediate may be found in sections VII.A.2, VII.C.10.b, VII.F.1, and VII.F.5.

a. To Ethylenes

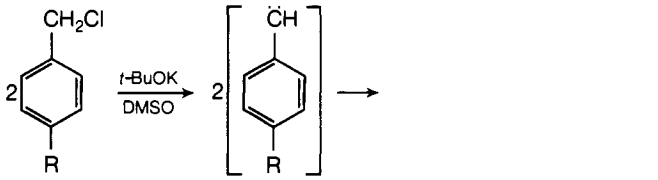
Hine and coworkers[170] synthesized a mixture of the cis and trans forms of 1,2-difluoro-1,2-di-*tert*-butoxyethylene (**267**) from dichlorofluoromethane (**265**) through the carbene **266** (eq 157). It appears that stilbenes **269** are produced by the same mechanism from chloromethylbenzenes[171] (**268**) (eq 158).



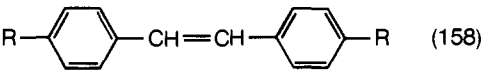
(157)

b. To Cyclopropanes and Norcaranes

Many cyclopropanes[172] and norcaranes[169,172b,173] have been synthesized through the carbene. An example of the former is 1-dimethylvinylidene-2-phenylcyclopropane[172a] (**271**) prepared from 1-chloro-3-methyl-1,2-butadiene (**270**) (eq 159). The *tert*-butoxide is the preferred



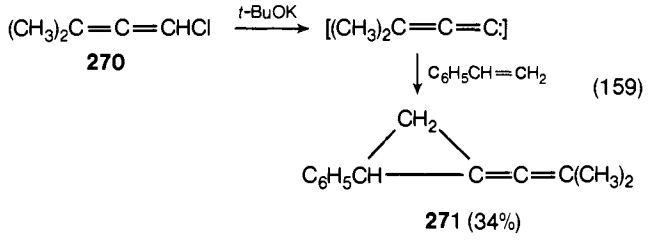
268



269 (36–51%)

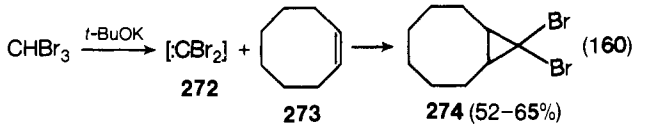
R = H, CH_3

base in the reaction. Sodium hydride in mineral oil was ineffective and butyllithium reacted with the alkenylidenecyclopropanes formed.



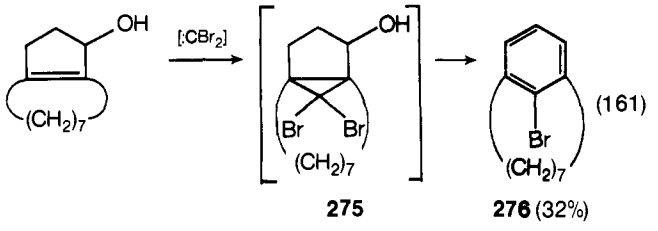
270 271 (34%)

An example of the norcarane-type synthesis is that of 9,9-dibromobicyclo[6.1.0]nonane[173a] (**274**) produced from cyclooctene (**273**) *via* the carbene (**272**) (eq 160).



272 273 274 (52–65%)

Isomerization of the intermediate dibromocyclopropane (**275**) may occur to form the aromatic species[174] (**276**) (eq 161).



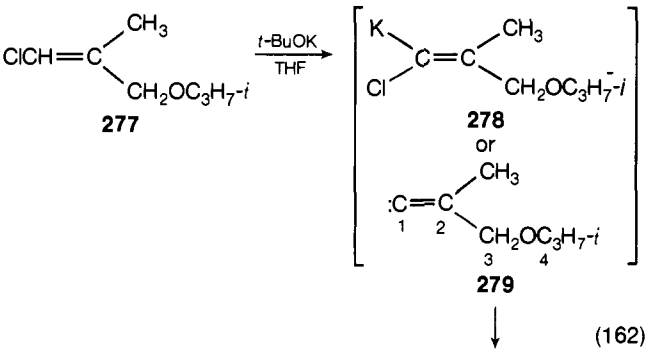
275 276 (32%)

c. To 2,5-Dihydrofurans or 2,5-Dihydropyrrolines

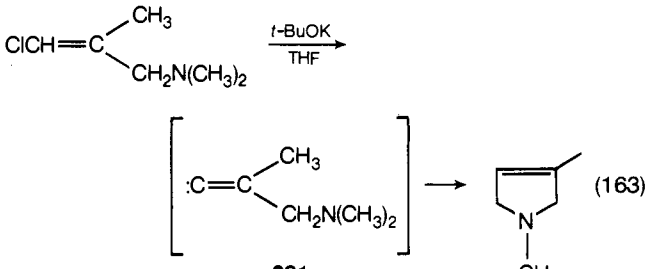
Walsh and Bottini[175] subjected the *cis*- and *trans*-1-halo-2-methyl-3-alkoxy-1-propenes to the *tert*-butoxide and obtained usually the 2,5-dihydrofuran and the 2-methyl-3-*tert*-butoxy-3-alkoxypropene as the major products. For the *cis*-1-chloro-2-methyl-3-isopropoxy-1-propene (**277**), these investigators regarded the 2,5-dihydrofuran (**280**) as having originated either through the organometallic carbenoid **278** or the carbene **279** (eq 162). In a similar manner, 1-halo-2 methyl-3-alkylaminopropenes usually led to the corresponding 3-pyrroline as the chief product (eq 163). Again perhaps the alkylidene carbene **281** inserts in this case into an α C–H bond of the N–CH_3 group.

d. To Hydroxycyclopropenones

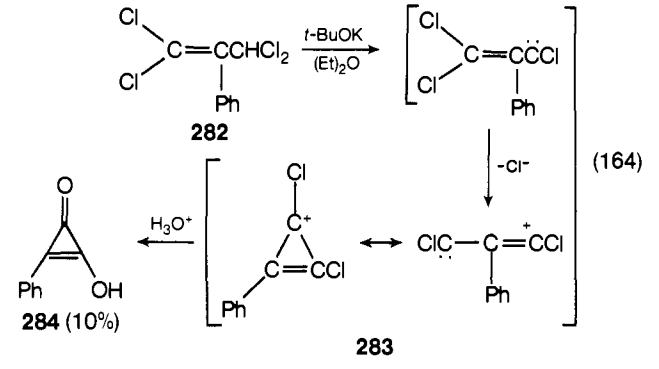
Farnum and Thurston[176] treated 2-phenyltetrachloropropene (**282**) with the *tert*-butoxide and obtained a small yield of phenylhydroxycyclopropenone (**284**) presumably through the carbene **283** (eq 164).



277 278 279 280 (33%) 32%



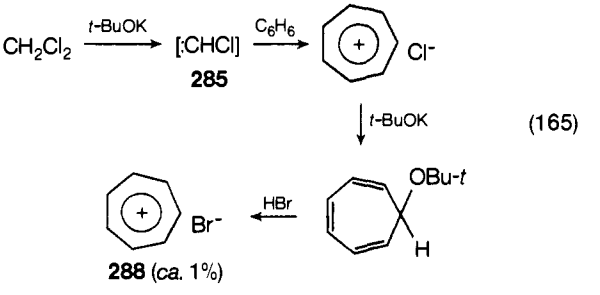
281 (36%)



282 284 (10%) 283

e. To Tropylium Bromide

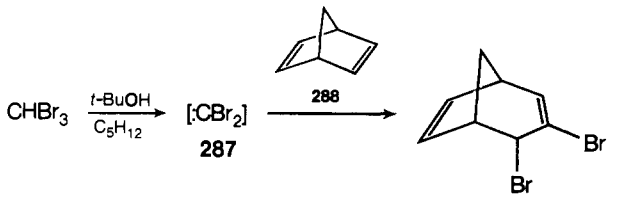
Volpin and coworkers[177] obtained a small amount of tropylium bromide (**286**) from methylene chloride and benzene *via* the carbene **285** (eq 165).



285 288 (*ca.* 1%)

f. To 3,4-Dibromobicyclo[3.2.1]octa-2,6-diene

The enlargement of one of the rings of norbornadiene (**288**) to form 3,4-dibromobicyclo[3.2.1]octa-2,6-diene (**289**) was accomplished by Baldwin and Foglesong[178] *via* the carbene **287** (eq 166).

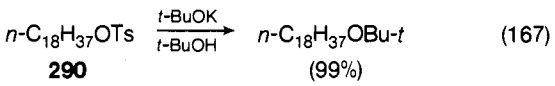


289 (40%) (166)

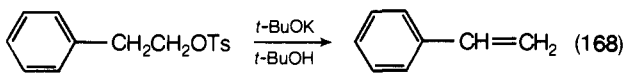
D. Dehydrotosylation or Dehydromesylation

1. To Alkenes and Dienes

Arnold and coworkers[131] have shown that the *tert*-butoxide with the tosylate of a higher primary alcohol (**290**) gives essentially substitution while the tosylate of a β-aryl substituted alcohol (**291**) gives largely elimination, eq 167 and 168, respectively. The latter reaction illustrates the very delicate balance that exists between elimination and displacement. Whatever forces control this balance, the greater acidity of the β-hydrogen of **291** and/or the greater stability of styrene change complete displacement in **290** to complete elimination in **291**.



290 (99%) (167)

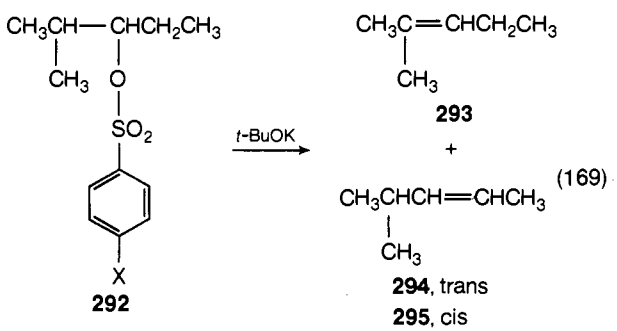


291 (100%) (168)

Snyder and Soto[179] obtained both alkenes and *tert*-butyl ethers from the tosylates of a great variety of simpler alcohols and *t*-BuOK in DMSO at room temperature. The highest yields of alkenes, about 80%, were formed from esters of cyclic and secondary acyclic alcohols. On the other hand, esters of primary alcohols and cyclohexanol gave 20–25% of alkenes and 60–70% of ethers.

In a study of the tosylates of 2-butyl and 2-pentyl alcohols with the *tert*-butoxide in *tert*-butyl alcohol, Froemsdorf and coworkers[180] found that in each case the 1-alkene was the major product, 64 and 73%, respectively, and more *cis*- than *trans*-2-alkene was produced. As in the elimination occurring in halides (see section VII.C.1 for an explanation), the *tert*-butoxide gives a higher percentage of the 1-alkene than KOC_2H_5, and the excess of the *cis*- over the *trans*-2-alkene was shown to be characteristic of nonpolar solvents in which the *tert*-butoxide exists in a more clustered state.

Colter and McKelvey[181] carried out the elimination reactions of 2-methyl-3-pentylarenesulfonates (**292**) using the *tert*-butoxide in various solvents (eq 169). The percentages of products are given in Table VII. The amount of cis olefin, **295**, was markedly less than that found (about 15–20%) in solvents without DMSO, the explanation for which has already been given (section VII.C.1). The rates in DMSO were much faster and quite



292 (169)

294, trans
295, cis

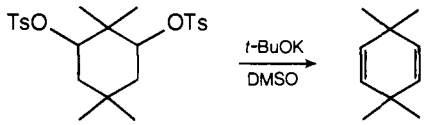
TABLE VII. Percentages of Alkenes Obtained from 292 with t-BuOK in 25% t-BuOH-DMSO

X	293	294	295
$(CH_3)_2N$	48	50	2
NO_2	61	36	3

sensitive to substituents (ρ = 2.4). For example, the *p*-bromo compound formed the olefin about eight times faster than the *p*-methyl compound.

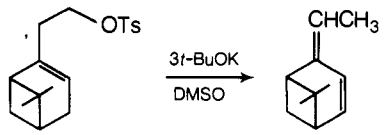
The dehydrotosylation of 5-decyl tosylate has been discussed in section VII.C.1, in order that the results of the two types of elimination may be considered together.

Reusch and Frey[182] were successful in preparing 1,1,4,4-tetramethyl-2,5-cyclohexadiene (**297**) in good yield from 1,1,4,4-tetramethyl-2,6-ditosylcyclohexane (**296**) (eq 170). The acetate pyrolysis procedure using the diacetate was not satisfactory because of thermal decomposition of the product to form *p*-xylene.

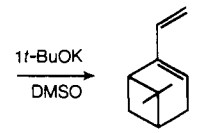


296 **297** (170)

In treating nopol tosylate (**298**) with 3 equiv of the *tert*-butoxide, Cupas and Roach[183] obtained 2-ethylidene-6,6-dimethylbicyclo[3.1.1]hept-3-ene (**299**) (eq 171). If 1 equiv of base is employed, nopadiene (**300**) is produced (eq 172).



298 **299** (85%) (171)

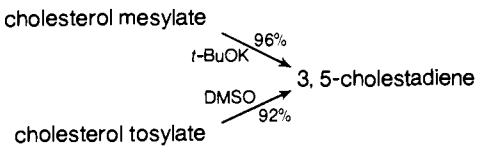


300 (65%) (172)

2. To Δ Steroids

It has already been shown (section VII.C.6) that 24-cholanyl tosylate gives largely the ether with the *tert*-butoxide and DMSO. A study by Chang[184] as given in Table VIII on a series of tosylates and mesylates lists exceptions. Thus the percentage of the ene is greater than that of the ol in all cases except those of the mesylates of 3β-cholestanol and 3α-cholanol. It is interesting to note the increase in the percentage of ene in the case of 3β-cholestanol mesylate with an increase in temperature.

High yields of dienes have been obtained from certain cholesterol derivatives[185] (eq 173).



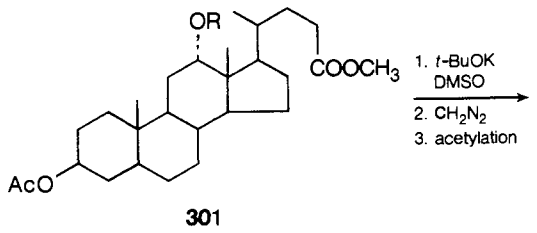
(173)

Δ^{11}-Steroids (**302**) have been prepared with the *tert*-butoxide and the tosylate and mesylate of methyl 3α-acetoxy-12α-hydroxycholanate[186] (**301**) (eq 174). Lower yields were obtained by replacing DMSO with *N*-methylpyrrolidone, sulfolane, or tetraethylene glycol dimethyl ether, or by substituting dimsylsodium for *t*-BuOK.

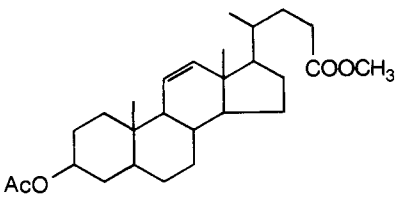
TABLE VIII. Products from the Action of *t*-BuOK–DMSO on the Tosylates and Mesylates of Sterols

Substrate	Temp, °C	% ene[a]	% β-ol
3β-Cholestanol mesylate	25	4	86
	56	67	19
3β-Cholestanol tosylate	25	57	17
3α-Cholestanol mesylate	25	77	14
3α-Cholestanol tosylate	25	68	9
3α-Cholanol mesylate	25	6	87

[a] Location of double bond was not given.



301



(174)

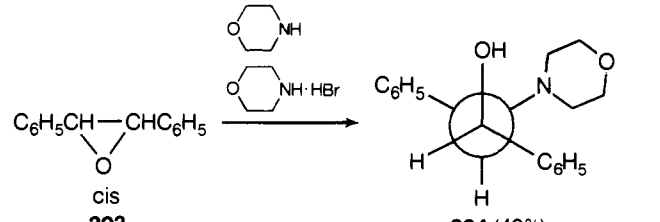
302

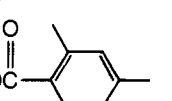
R = Ts ~74%; R = Ms ~55%

E. Other Eliminations

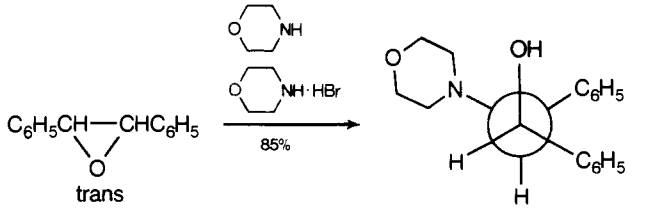
1. Loss of Carboxylic Acid Enamines

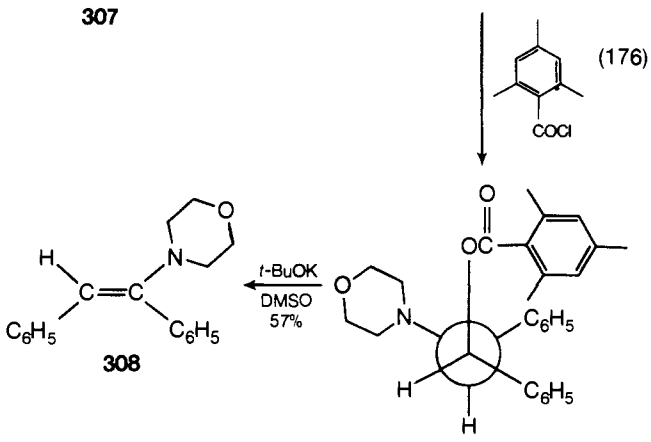
By taking advantage of the sterospecificity of the bimolecular β-elimination reactions, Munk and Kim[187] were able to synthesize cis and trans enamines. The cis epoxide **303** was first converted into morpholinodiphenylethanol (**304**) whose mesitoates (**305**) with the *tert*-butoxide gave the trans (**306**) enamines (eq 175). By a similar procedure the trans epoxide **307** was converted into the cis enamine **308** (eq 176).





(175)

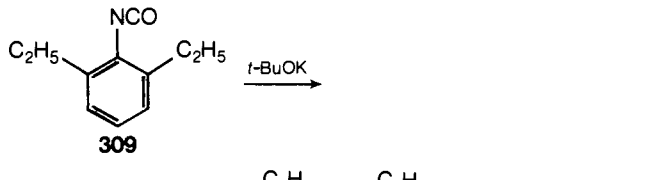




(176)

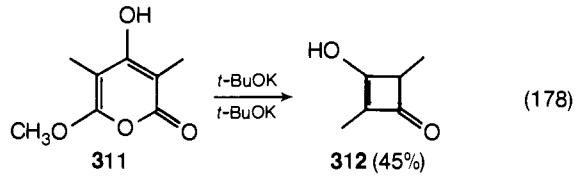
2. Loss of CO_2 or Its Derivatives

Bis(2,6-diethylphenyl)carbodiimide[189] (**310**) has been produced with the elimination of CO_2 by heating 2,6-diethylphenyl isocyanate (**309**) with the *tert*-butoxide (eq 177). Sodium methoxide was less satisfactory. In a second example, Corbella and coworkers[188] refluxed the α-pyrone **311** with the *tert*-butoxide and achieved ring contraction to 2,4-dimethyl-2-cyclobuten-3-ol-1-one (**312**) (eq 178). The method is an improvement over previous methods of synthesis.



(177)

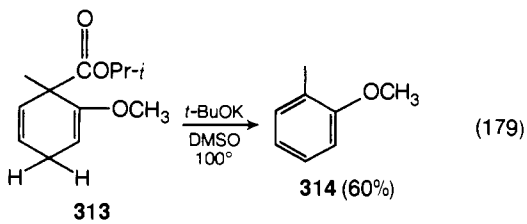
310 (90%)



(178)

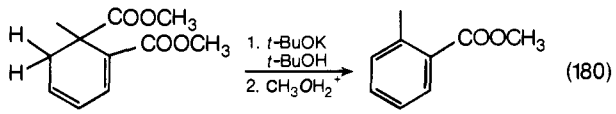
3. Loss of the Elements of a Formic Ester

Magid and coworkers[190] have shown that 2,5- (**313**) and 2,4-cyclohexadiene-1-carboxylates (**315**) with the



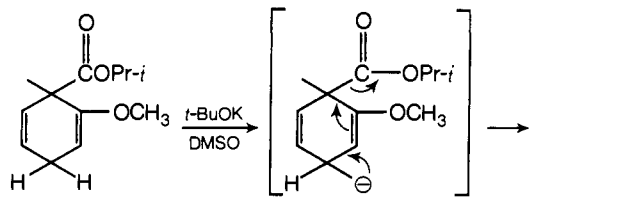
(179)

tert-butoxide are aromatized with the loss of a ring hydrogen and a carboxylate group to give the methylphenol (**314**) and ester (**316**), respectively (eq 179 and 180).

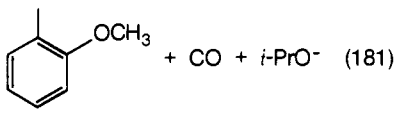


315 **316** (58%) (180)

The methyl ester rather than the isopropyl ester (eq 179) with lithium dimethylamide gives a quantitative yield of **314**. It appears that the formation of **314** occurs *via* the carbanion **317** (eq 181).



313 **317**

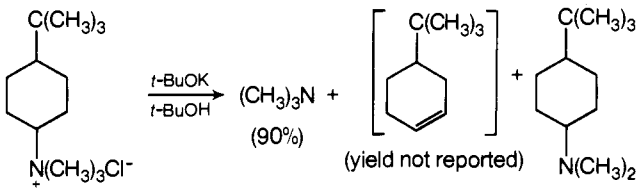


(181)

314

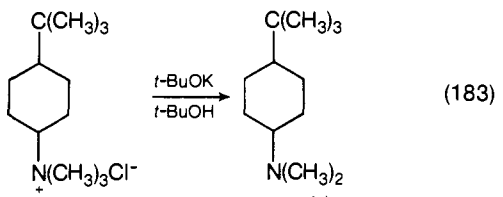
4. Loss of Tertiary Amines

Curtin and coworkers[191] treated *cis*- (**318**) and *trans*-4-*tert*-butylcyclohexyltrimethylammonium chloride (**319**) with the *tert*-butoxide to obtain 90% Hofmann elimination and 10% displacement with the former and 100% displacement with the latter, eq 182 and 183, respectively. The unsubstituted trimethylammonium chloride, on the other hand, gives 93% displacement and 7% Hofmann elimination.



cis
318

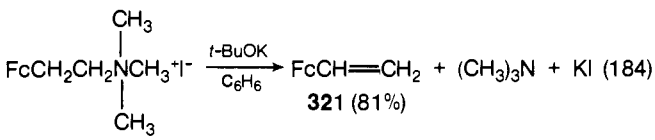
(182)



trans
319
(100%)

(183)

On refluxing (2-ferrocenylethyl)trimethylammonium iodide (**320**) with the *tert*-butoxide, Pauson and Watts[192] obtained vinylferrocene (**321**) (eq 184) in a yield improved over that of previous reports.

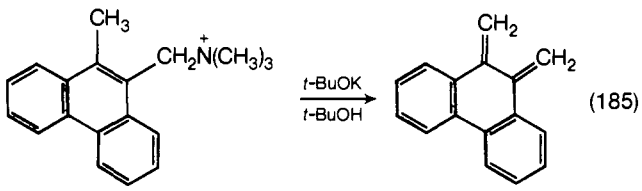


(184)

321 (81%)

320, Fc=ferrocenyl

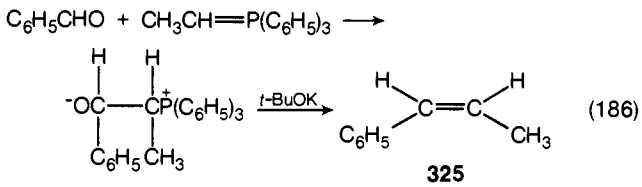
An interesting unstable diene, **323**, has been prepared in small amounts from the quaternary ammonium salt[193] **322** (eq 185). With irradiation the diene cyclizes to 9,10-cyclobutenophenanthrene.



322 **323** (185)

5. Loss of Triphenylphosphine Oxide

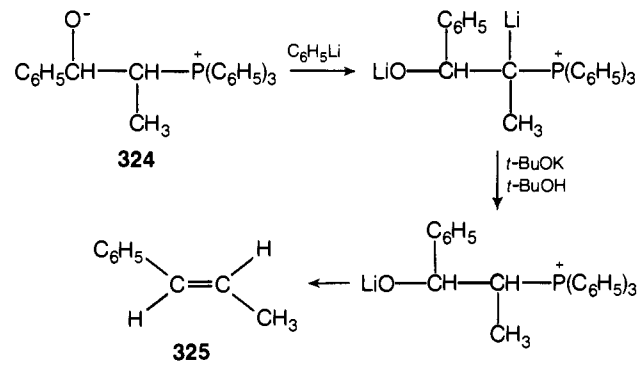
The *tert*-butoxide plays an important role in controlling the stereospecific synthesis of olefins from phosphoranes.[194] For example, for nonstabilized phosphoranes (**324**) salt-free, nonpolar solvents favor cis olefins[195] (**325**) (eq 186). However, if the betaine **324** is treated



324 **325**
(98%, 87% cis)

(186)

first with phenyllithium, the trans olefin **325** is formed (eq 187). The intermediates which lead to the respective alkenes in eq 186 and 187 must have the opposite configurations.



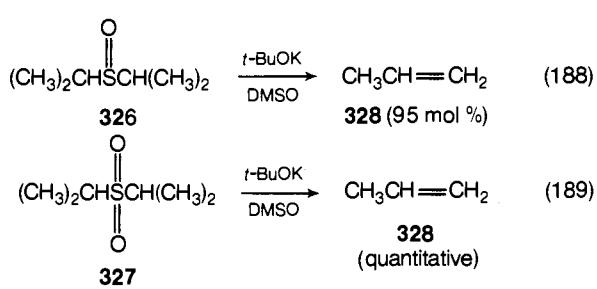
324

325
(69%, 97% trans)

(187)

6. Loss of Sulfenic or Sulfinic Acids

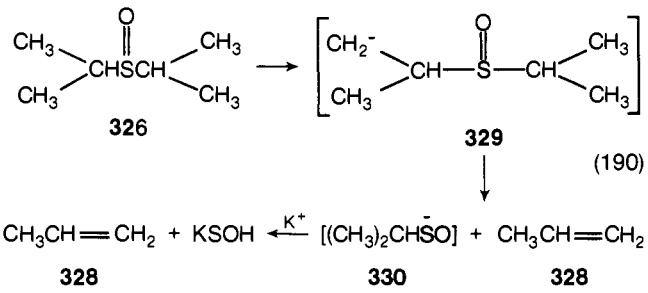
Eliminations from acyclic sulfoxides and sulfones are noteworthy in that the yields are often high. Schriesheim and coworkers[196] found that the *tert*-butoxide in DMSO is the preferred reagent and that sulfones are degraded more readily than sulfoxides. Among the acyclic sulfoxides **326**, and sulfones (**327**), the better yields of alkene (**328**) are obtained from those having branched alkyl groups, eq 188 and 189, respectively.



326 **328** (95 mol %) (188)

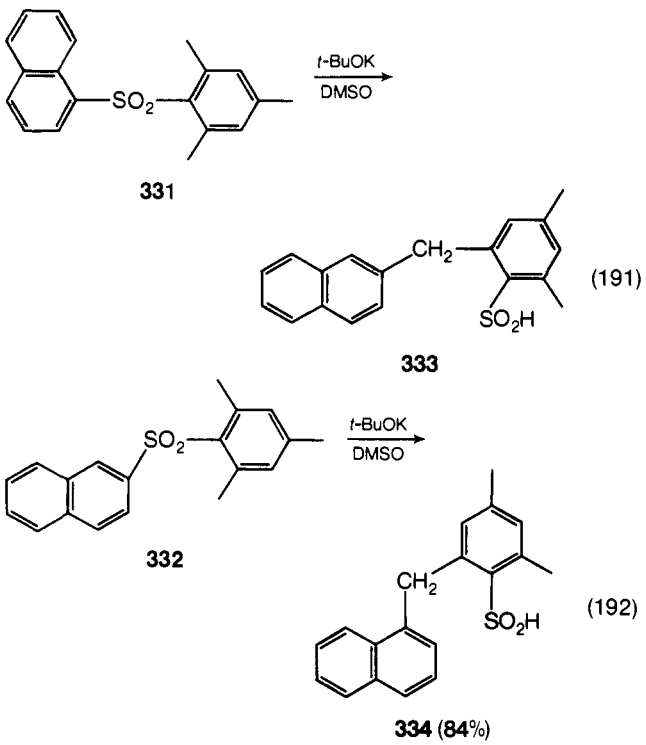
327 **328** (quantitative) (189)

The mechanism[196] appears to involve a carbanion (**329**) which by elimination forms an alkene (**328**) and an alkyl sulfenate ion (**330**). The latter with the base produces a second molecule of the alkene **328**, eq 190.



(190)

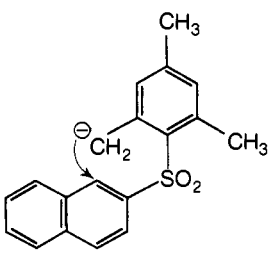
It is obvious that diaryl sulfones will not yield alkenes as the dialkyl sulfones do. In fact, Truce and coworkers[197] have shown that when mesityl 1- (**331**) and mesityl 2-naphthyl (**332**) sulfones are treated with the *tert*-butoxide, rearrangements occur to give 2-(2'-naphthylmethyl)- (**333**) and 2-(1'-naphthylmethyl)-4,6-dimethylbenzenesulfinic acids (**334**), eq 191 and 192, respectively.



(191)

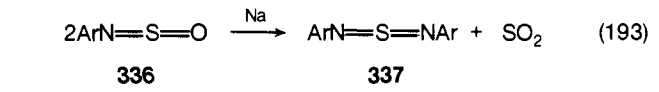
(192)

ly. The products indicate a cyclic mechanism in which the CH_2^- of the carbanion **335** attacks the naphthalene ring.



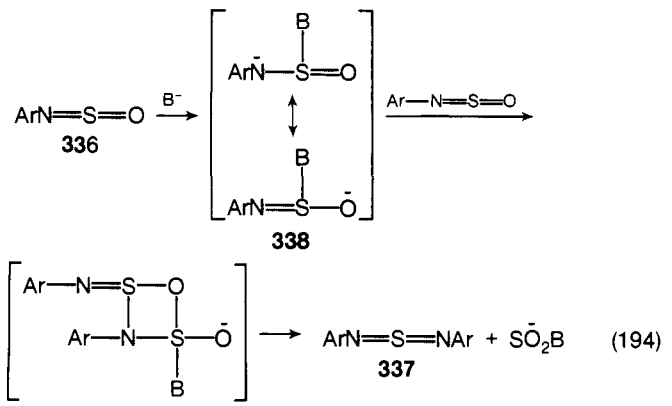
7. Loss of SO_2 or SO_2 and HCl

In the synthesis of diarylsulfurdiimides (**337**) from *N*-sulfinylanilines (**336**) (eq 193), low yields are obtained by



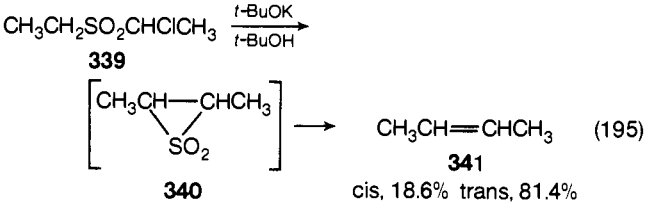
(193)

the use of sodium. Hörhold and Beck[198] showed that improved yields are possible with the *tert*-butoxide, $NaOC_2H_5$, or $NaNH_2$ in benzene, DMF, or diisopropyl ether at room temperature. In a series of syntheses, yields with the first reagent ran 50–95%, with the second 60–75%, and with the third 74–82%. It is proposed that an anion **338** is formed as an intermediate in the reaction (eq 194).



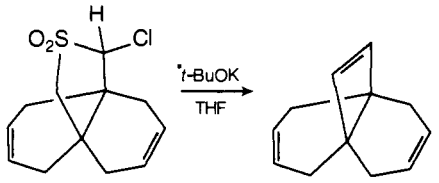
(194)

Loss of both SO_2 and HCl may occur from α-chloro sulfones **339** usually *via* the Ramberg–Bäcklund three membered ring intermediate[199] **340**, to give the alkene **341** (eq 195). When the possibility of cis–trans isomerism exists as in eq 195, most bases give an excess of the cis form. However, the *tert*-butoxide in *tert*-butyl alcohol is an exception in that more trans than cis is obtained.



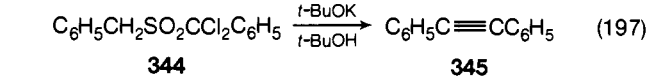
(195)

Another example is that of the α-chloro sulfone **342** which with the *tert*-butoxide gives the cyclobutene[200] **343** (eq 196). With dilute NaOH the starting material was re-



(196)

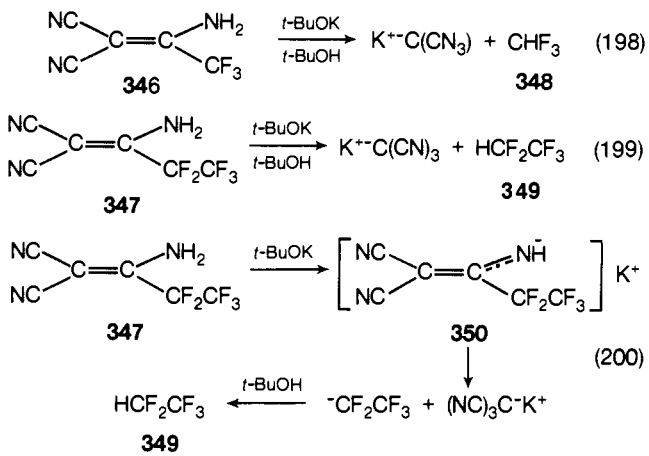
covered unchanged. Similarly α,α-dichlorobenzyl benzyl sulfone (**344**) with the *tert*-butoxide gives the acetylene[201] **345** (eq 197).



(197)

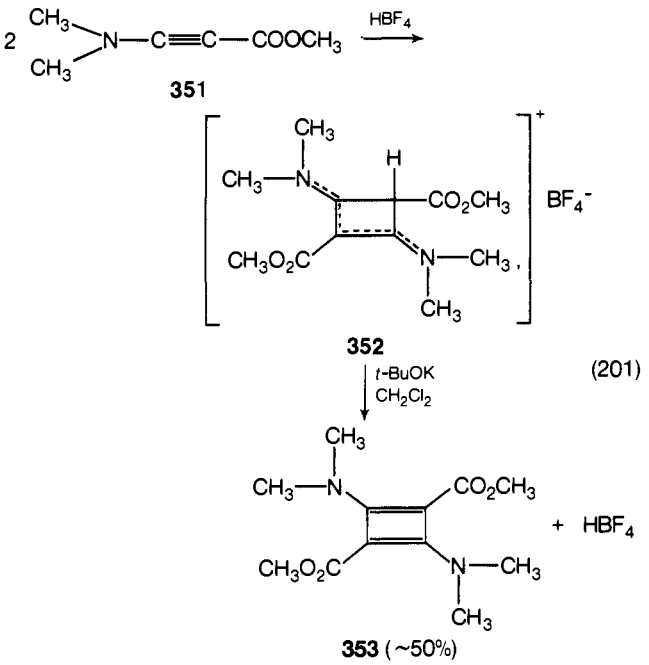
8. Loss of Fluoroalkanes

On treatment of 1-amino-1-trifluoromethyl-2,2-dicyanoethylene (**346**) and 1-amino-1-pentafluoroethyl-2,2-dicyanoethylene (**347**) with the *tert*-butoxide, Josey[202] obtained fluoroform (**348**) and pentafluoroethane (**349**) (eq 198 and 199, respectively) in unstated yields. It has been proposed that the elimination proceeds through a carbanion **350** (eq 200).



9. Loss of Hydrogen Tetrafluoroborate

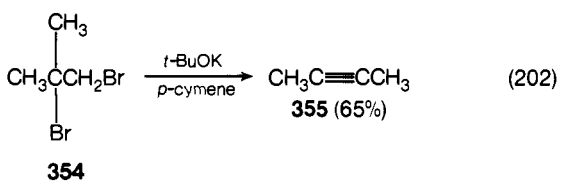
On treatment of dimethylaminocarbomethoxyacetylene (**351**) with fluoroboric acid, Neuenschwander and Neiderhauser[203] obtained a salt **352**, which with the *tert*-butoxide produced dimethyl 2,4-bis(dimethylamino)cyclobutadiene-1,3-dicarboxylate (**353**) and fluoroboric acid (eq 201). In the last step it is important to avoid an excess of base. Another loss of HBF_4 is illustrated in eq 155.



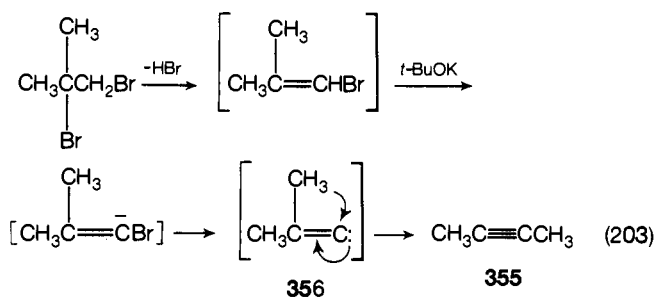
F. Dehydrohalogenation with Rearrangement

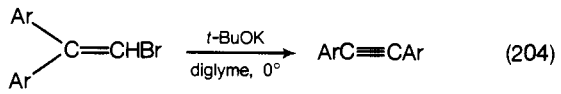
1. To Alkynes

Wolinsky[204] in treating 1,2-dibromo-2-methylpropane (**354**) with the *tert*-butoxide obtained 2-butyne (**355**) (eq 202). The mechanism appears to involve the carbene **356** (eq 203).

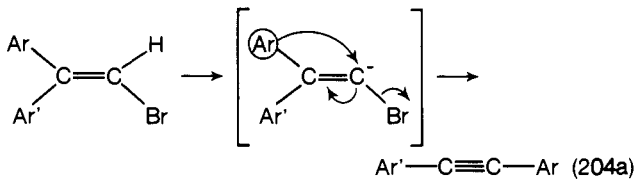


Similarly a series of alkynes **358** has been prepared by Bender and coworkers[205] by the treatment of 1,1-diaryl-2-bromoethenes (**357**) (eq 204) with the *tert*-butoxide. When Ar = C_6H_5, *m*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-FC_6H_4, and *p*-$CH_3OC_6H_4$, satisfactory amounts of the alkyne are obtained. However when Ar = *m*- or *p*-$CF_3C_6H_4$, none of the alkyne is obtained, but instead the product is the bis(trifluoromethylphenyl)vinyl *tert*-butyl ether.



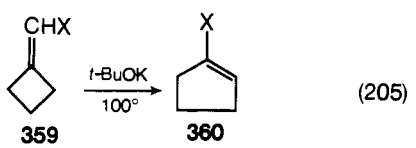


The mechanism of acetylene formation (Fritsch–Buttenberg–Wiechell rearrangement) here[205a] is given in eq 204a.



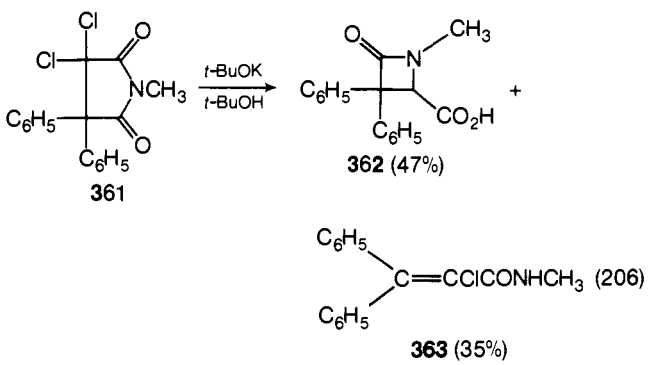
2. To Halocyclopentenes

With halomethylenecyclobutanes (**359**), Erickson and coworkers[206] discovered that ring expansion occurs, probably *via* elimination of HX followed by readdition, to give halocyclopentenes (**360**) (eq 205). On small-scale runs the yields of halocyclopentenes were in the 80–90% range. *n*-Butyllithium, sodamide, and molten potassium hydroxide behave similarly to the *tert*-butoxide, but sodium hydride is ineffective.

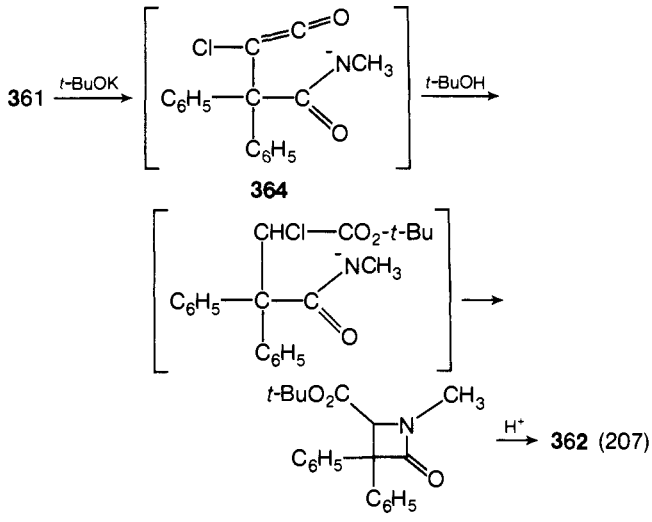


3. To β-Lactams and α-Chloroacrylamides

Chasle and Foucaud[207] subjected *N*-methyl-α,α-dichloro-α′,α′-diphenylsuccinimide (**361**) to the *tert*-butoxide to obtain the β-lactam **362** and the α-chloroacrylamide **363** (eq 206). These two types were also produced with $NaOCH_3$ in yields varying with the type of substituents present in the succinimide and the solvent used.



The mechanism appears to proceed *via* the ketene **364** (eq 207).

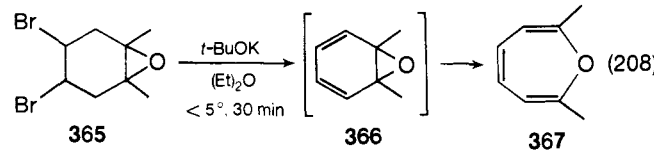


364

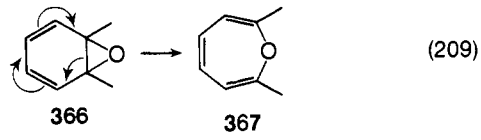
362 (207)

4. *To 2,7-Dimethyloxepin, 2-Alkoxy-7-tert-butoxy-6-halo-2,3,4,7-tetrahydrooxepins, and 1,5-Dibromo-4a,9a:8a,10a-diepoxy-1,4,5,8,9,10-hexahydroanthracene*

Paquette and Barrett[208] synthesized 2,7-dimethyloxepin (**367**) by the dehydrobromination and rearrangement of 4,5-dibromo-1,2-dimethyl-1,2-epoxycyclohexane (**365**) (eq 208). The method is a general one for the preparation of oxepins. The mechanism probably proceeds from the intermediate **366** as in eq 209.

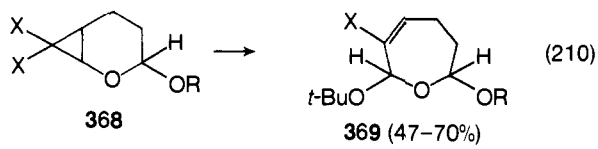


365 **366** **367** (208)



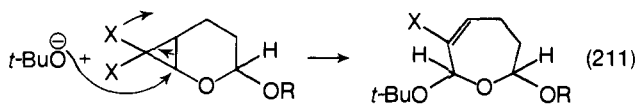
366 **367** (209)

Somewhat similarly, Thuy and Maitte[209] have shown that 3-alkoxy-7,7-dihalo-2-oxabicyclo[4.1.0]heptanes (**368**) are dehydrohalogenated with rearrangement to form 2-alkoxy-7-*tert*-butoxy-6-halo-2,3,4,7-tetrahydrooxepins (**369**) (eq 210). These events suggest cyclopropane splitting (eq 211).



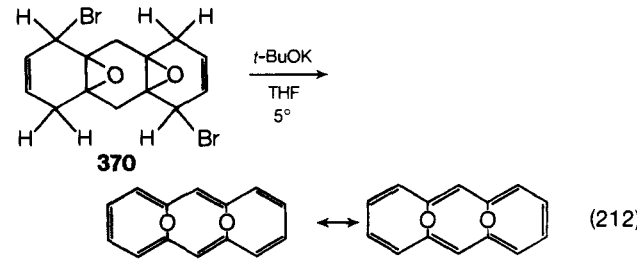
368 **369** (47–70%) (210)

X = Cl or Br, R = alkyl



369 (211)

A third case involving the splitting of a three-membered ring is that of 1,5-dibromo-4a,9a:8a,10a-diepoxy-1,4,5,8,9,10-hexahydroanthracene (**370**). With the *tert*-butoxide Vogel and coworkers[210] obtained a low yield of what was probably *syn*-1,6:8,13-diepoxy[14]annulene (**371**) (eq 212). The mechanism is similar to that given for the first case, that of **365.**

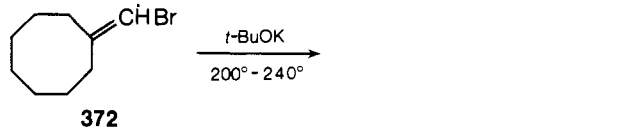


370 (212)

371

5. *To Cycloalkynes and tert-Butyl Ethers of Endocamphane*

It is shown (section VII.F.2) that with the *tert*-butoxide bromomethylenecyclobutane loses hydrogen bromide which then adds to give a bromocyclopentene. Higher membered cycloalkanes, such as bromomethylenecyclooctane[211] (**372**) instead lose hydrogen bromide and then rearrange to give a total 65% yield of cyclononyne (**373**), 1,3-cyclononadiene (**374**), 1,2-cyclononadiene (**375**), and bicyclo[6.1.0]non-1(2)-ene (**376**) (eq 213). Of particular interest here is the fact that highly strained cyclic acetylenes such as cyclohexyne and cyclopentyne, generated from their respective bromomethylene derivatives by *t*-BuOK, are captured in 35 and 12% yields, respectively, by 1,3-diphenylbenzofuran.



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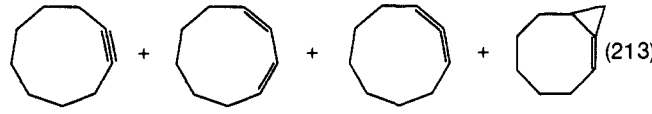
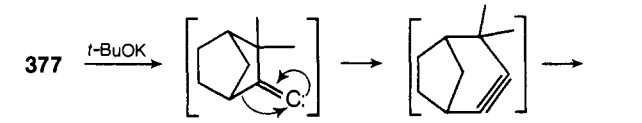


373	**374**	**375**	**376**
(9%)	(25%)	(27%)	(40%)

(213)

On treating ω-bromocamphane (**377**) with the *tert*-butoxide Wolinsky[204] found that dehydrohalogenation occurred with ring expansion to form the enol ethers **378** and **379** in essentially quantitative yield (eq 214) in a 2:1 ratio, respectively. Although KOH gave similar results, the *tert*-butoxide exhibits greater specificity. The intermediate formation of the endocamphyne (**380**) was shown

377 **378** **379** (214)



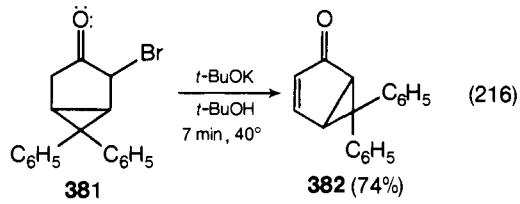
380

378 + **379** (215)

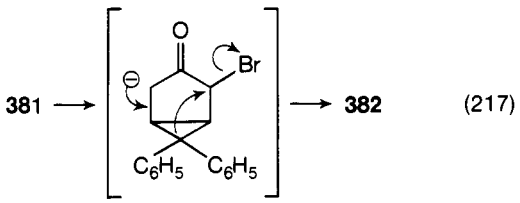
by the fact that this alkyne could be trapped with 1,3-diphenylisobenzofuran.[204b] This fact suggests that the mechanism may be that given in eq 215.

6. To 6,6-Diphenylbicyclo[3.1.0]hex-3-en-2-one

Zimmerman and coworkers[212] discovered that 2-bromo-6,6-diphenylbicyclo[3.1.0]hexan-3-one (**381**) is converted into 6,6-diphenylbicyclo[3.1.0]hex-3-en-2-one (**382**) by the butoxide (eq 216). The mechanism is represented *via* cyclopropane ring opening in eq 217.



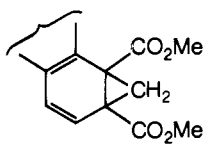
381 **382** (74%) (216)



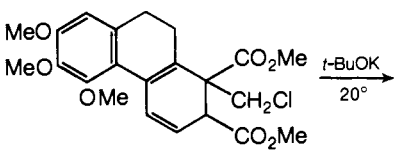
(217)

7. To a Dimethyl Cycloheptatrienedicarboxylate

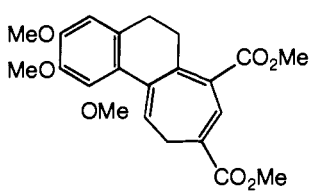
Small carbocyclic rings attached to larger rings may rearrange to form a single ring. Such a rearrangement occurs in the synthesis of colchicine[213] in the course of which a six-membered ring of **383** is expanded to form a seven-membered ring of **384** (eq 218). The intermediate here is doubtless the norcarane



in the formation of which the *tert*-butoxide is a common reagent (see section VII.C.11).



383



(218)

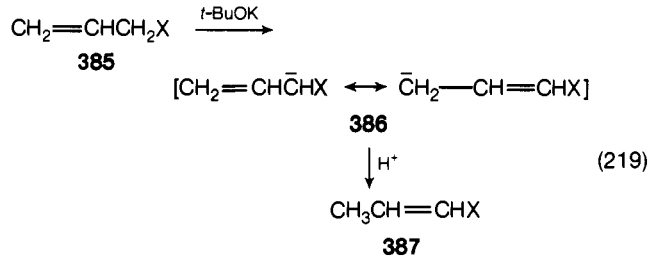
384 (88%)

VIII. Isomerization

Potassium *tert*-butoxide has been used widely in isomerization, particularly of unsaturated compounds. Indeed the isomerization reaction has been so reliable that it has been utilized to determine the efficacy of a wide variety of base–solvent systems.[15]

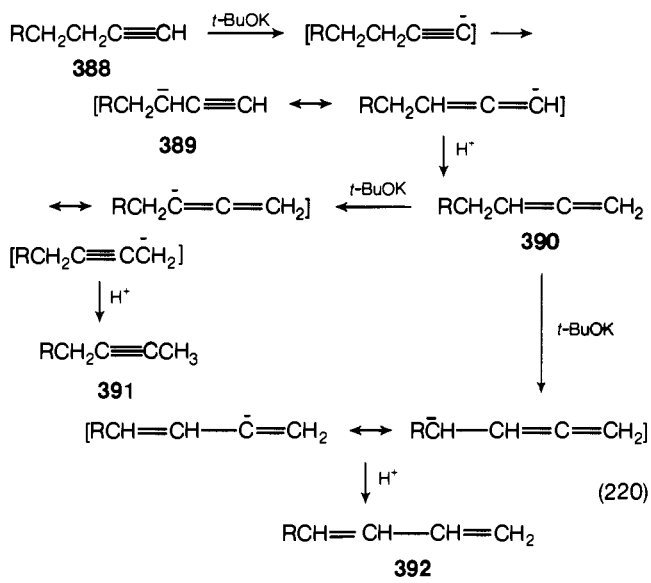
A. Mechanism and Generalizations

Base-promoted isomerizations, as has been shown repeatedly, are regarded as occurring through a carbanion generated by the base,[214] Thus the isomerization of an allyl type **385** probably occurs through the resonating carbanion **386** which adds a proton to give the isomeric type **387** (eq 219).



(219)

In the case of alkynes the mechanism is somewhat more complicated in order to account for a greater variety of products. Smadja[215] utilizes the carbanion **389** to explain the formation of an allene (**390**), a 2-alkyne (**391**), and a 1,3-alkadiene (**392**) from a 1-alkyne (**388**) (eq 220).



(220)

Since the alkenes are not held as carbanions in the presence of the *tert*-butoxide, but rather merely isomerize *via* the carbanion, the isomerization produces the most thermodynamically stable alkene. Thus mixtures may be the end result of isomerization because the alkenes do not differ greatly in their stabilities. Nevertheless, in the main, the following preponderant products may be expected by anionic catalysis.

allyl ethers or amines → vinyl ethers or amines

terminal alkenes or alkynes → non-terminal alkenes or alkynes

nonconjugated dienes → conjugated dienes

cumulenes → acetylenes

enynes → conjugated trienes

dienes → aromatics and dienynes

B. Enes

One of the earliest migrations studied was that of the double bond in allyl ethers (**393**) to form propenyl ethers[216] (**394**) (eq 221). The reaction is stereospecific in that cis forms are obtained with monoallyl ethers as

well and the isomerization is suggested as a method for preparing propenyl ethers.

$$CH_2{=}CHCH_2OCH_2(CH_2)_3CH_2OCH_2CH{=}CH_2 \xrightarrow[48\ hr]{t\text{-BuOK},\ 150^\circ}$$

393

$$CH_3CH{=}CHOCH_2(CH_2)_3CH_2OCH{=}CHCH_3 \quad (221)$$

394

cis–cis 97% (94.9% recovered)

Price and Snyder[217] investigated the simpler allyl ethers. Their results (eq 222) agree with those of Prosser. When R = C_6H_5, the phenyl propenyl ether was obtained in 99% yield and 99% of the isomer was cis.

$$CH_2{=}CHCH_2OR \xrightarrow[DMSO]{t\text{-BuOK}} CH_3CH{=}CHOR \quad (222)$$

The allylamines respond similarly[218] (eq 223). When R_2 = Me_2, Et_2, Pr_2, $i\text{-}Pr_2$, the product consists of a mixture of cis and trans forms containing 60–93% of the cis.

$$CH_2{=}CHCH_2NR_2 \xrightarrow[DMSO]{t\text{-BuOK}} CH_3CH{=}CHNR_2 \quad (223)$$

That certain 1-substituted 2-alkenes isomerize to the 1-alkenes has also been pointed out by Kesslin and Orlando[219] (eq 224). This conversion was almost complete when X = OC_2H_5, SC_2H_5, or $N(CH_3)_2$.

$$CH_2{=}CHCH_2X \xrightarrow[DMSO\ or\ DME]{t\text{-BuOK}} CH_3CH{=}CHX \quad (224)$$

With unsubstituted 1-alkenes, the 2-isomers are favored[220] as shown in eq 225. The branched-methyl 1-alkenes respond similarly[214a] (eq 226). If a phenyl group is

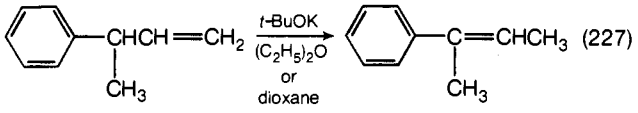
$$CH_3CH_2CH{=}CH_2 \xrightarrow[HMPA]{t\text{-BuOK}} CH_3CH{=}CHCH_3 \quad (225)$$

(80% conversion; 76% cis, 4% trans)

$$CH_3CH_2CH_2C(CH_3){=}CH_2 \xrightarrow[DMSO,\ 55^\circ]{t\text{-BuOK}} CH_3CH_2CH{=}C(CH_3)CH_3 \quad (226)$$

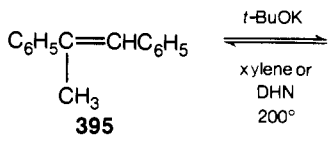
(88.1%)

introduced into the alkene as in 3-phenylbutene-1, the equilibrium also lies far to the right[11] (eq 227). In this case the catalytic activity of potassium methoxypolyethylene glycolate exceeds that of the *tert*-butoxide.



(227)

With *cis*-1,2-diphenylpropene (**395**), Zwierzak and Pines[221] found that isomerization occurs largely to the trans isomer **396** (eq 228). At times when a variety of isomers are formed at equilibrium, one may be present in



395

(cis, 21.0%)

$$C_6H_5\overset{2}{C}(CH_3){=}\overset{3}{C}HC_6H_5 + C_6H_5\overset{3}{C}H_2\overset{2}{C}(C_6H_5){=}\overset{1}{C}H_2 \quad (228)$$

396

(trans, 76.8%) (2.2%)

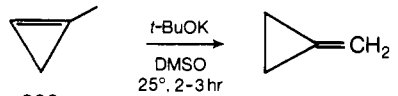
large amounts, and thus an unexpected source of the isomer becomes available. In this manner Doering and Bragole[222] found that *trans*-1-phenylbutene-2 with the *tert*-butoxide in *tert*-butyl alcohol exists in eight isomeric forms, some of which are o-propenyltoluenes. At 55° 92% of the mixture was *trans*-1-phenylbutene-1.

In a 1-alkene containing selenium (**397**), 100% isomerization occurs[223] to give the 2-alkene **398** (eq 229). Here the *tert*-butoxide was more effective than the sodium alkoxide of ethyl, isopropyl, *n*-butyl, *tert*-butyl, or *n*-amyl alcohol.

$$C_6H_5SeCH_2CH{=}CH_2 \xrightarrow[DMSO]{t\text{-BuOK}} C_6H_5SeCH{=}CHCH_3 \quad (229)$$

397 **398** (91% trans)

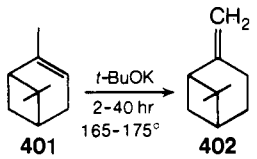
In the case of 1-methyl-1-cyclopropene, Krull and Arnold[224] found that the *tert*-butoxide in catalytic amounts gives methylenecyclopropane (**400**) (eq 230).



(230)

399 **400** (95%)

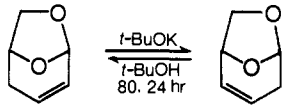
Among the terpenes, α-pinene[225] (**401**) gives β-pinene (**402**) (eq 231) with about 20% resinification. In addition, the rate of isomerization of 2-methylbicyclo[2.1.2]heptadiene-2,5 to 5-methylenebicyclo[2.1.2]heptene-2 by the *tert*-butoxide in DMSO is increased by the addition of an 18-crown-6-ether.[226]



(231)

401 **402**

Murray and coworkers[227] studied the equilibrium existing between 6,8-dioxabicyclo[3.2.1]oct-3-ene (**403**) and its 2-ene isomer (**404**). They found that with the *tert*-butoxide (eq 232), **403** gives a 49% yield of a mixture containing 80% of **404.** The latter is of value in preparing 2-deoxy- and dideoxy-DL-hexoses.



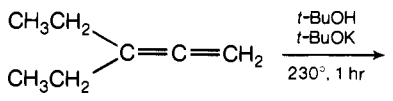
(232)

403 **404**

C. Dienes

Unconjugated dienes often isomerize to conjugated ones. Thus methyl linoleate, methyl linolenate, and safflower oil with the *tert*-butoxide in DMSO or DMF give largely the conjugated esters.[228] As a matter of fact, mixtures of linoleic and linolenic acids in natural oils may be analyzed spectrophotometrically since the absorptivities with the *tert*-butoxide reach a constant maximum.[229]

1,1-Diethylallene (**405**) forms *cis*- and *trans*-3-ethyl-1,3-pentadiene[230] (**406**) (eq 233), and 1,5-cyclooctadiene (**407**) and 1,2-cyclononadiene[231] (**408**) are con-

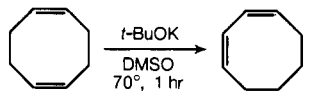


405

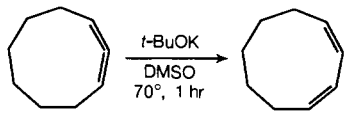
$$CH_3CH{=}C(C_2H_5){-}CH{=}CH_2 \quad (233)$$

406 (100%)

verted almost quantitatively intc 1,3-dienes **409** and **410** (eq 234 and 235), respectively.

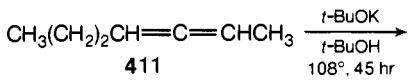


407 **409** (234)

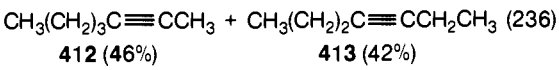


408 **410** (235)

Some allenes or unsaturated Schiff bases respond differently. For example, heptadiene-2,3 (**411**) gives a mixture of 2-heptyne (**412**) and 3-heptyne[232] (**413**) (eq 236).

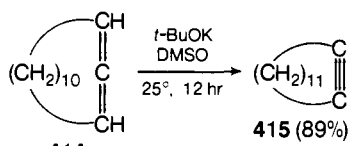


411



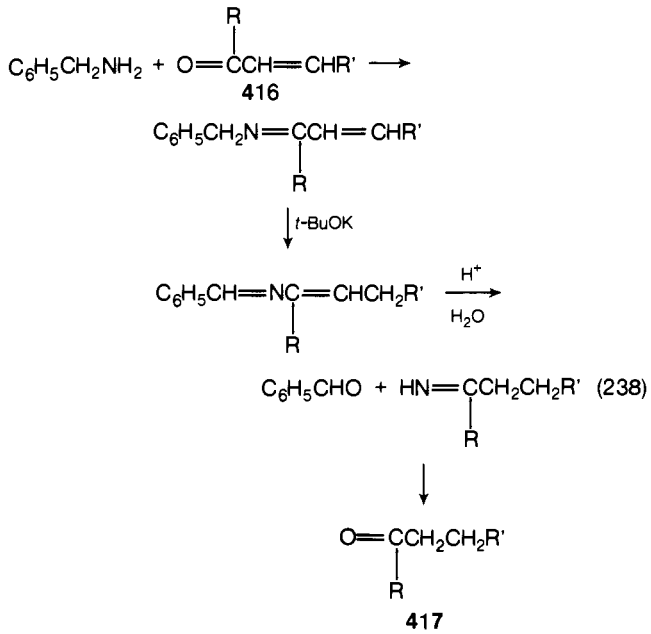
412 (46%) **413** (42%) (236)

In the cyclic series, cyclotrideca-1,2-diene (**414**) forms cyclotridecyne[233] (**415**) (eq 237). The latter isomerization failed to occur with the *tert*-butoxide in *tert*-butyl alcohol, with KOH in ethanol, with CH_3Li, or with basic alumina.



414 **415** (89%) (237)

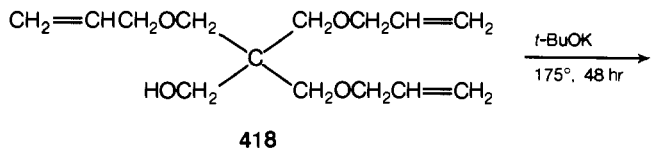
A Schiff base containing the $-N{=}CRCH{=}$ group isomerizes to one containing the $=N{-}CR{=}CH-$ group[234] in the presence of the *tert*-butoxide. This isomerization has been utilized in the selective reduction of compounds containing a double bond conjugated to the keto group (**416**) (eq 238). Thus the unsaturated ketone (**416**) produces the saturated one (**417**).



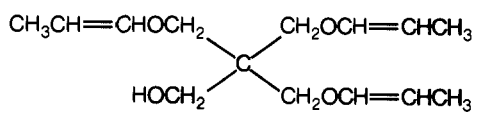
(238)

D. Trienes

Trienes also give a variety of products except in cases in which the double bonds are highly isolated, as in triallylic pentaerythritol (**418**) which isomerizes to the tripropenyl isomer[235] **419** (eq 239). The cumulene, 1-methoxy-

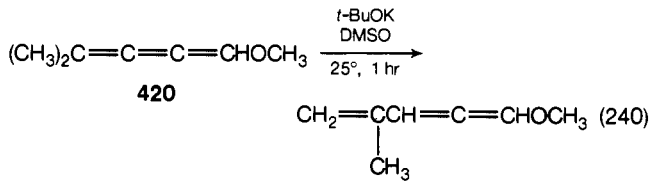


418



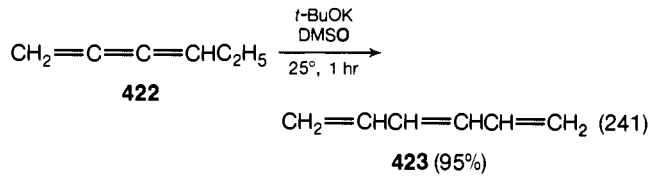
419 (86.1% conversion) (239)

4-methylpenta-1,2,3-triene (**420**), undergoes partial conjugation to give 1-methoxy-4-methylpenta-1,2,4-triene[236] (**421**) (eq 240). In some cases, as in 1,2,3-hexatriene



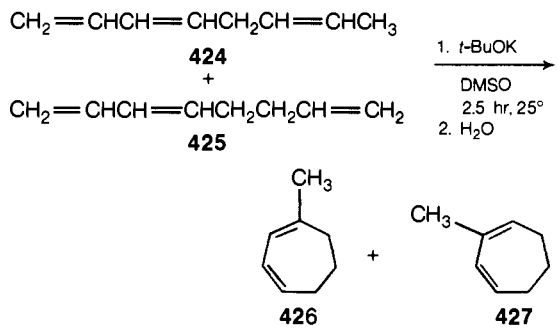
420 **421** (90%) (240)

(**422**), complete conjugation takes place to give the 1,3,5 isomer[236] **423** (eq 241). In other cases cyclization oc-



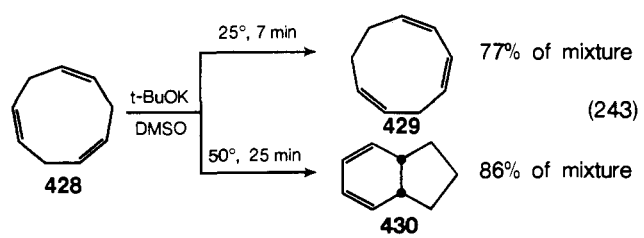
422 **423** (95%) (241)

curs. For example, a mixture of 60 mol % of 1,3,6- (**424**) and 40 mol % of 1,3,7-octatriene (**425**) produces a 34% yield of a mixture of predominantly 1-methyl- (**426**) and 2-methyl-1,3-cycloheptadiene[237] (**427**) (eq 242).



426 **427** (242)

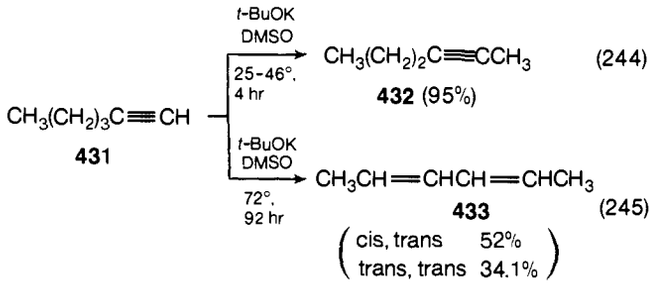
In the carbocyclic series Watthey and Winstein[238] found that *cis,cis,cis*-1,4,7-cyclononatriene (**428**) gives largely the *cis,cis,cis*-1,3,6- isomer (**429**) or *cis*-bicyclo-[4.3.0]nona-2,4-diene (**430**) depending on the experimental conditions employed (eq 243).



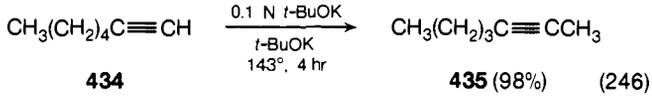
428 **429** **430** (243)

E. Alkynes

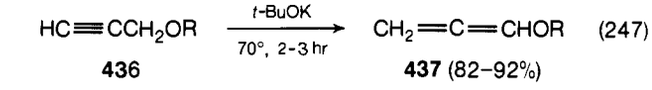
Alkynes may isomerize to other alkynes or to dienes. Thus Farmer and coworkers[239] found that 1-hexyne (**431**) isomerizes almost completely to 2-hexyne (**432**) under the conditions in eq 244, but under the conditions in eq 245 the product consists largely of conjugated dienes **433**.



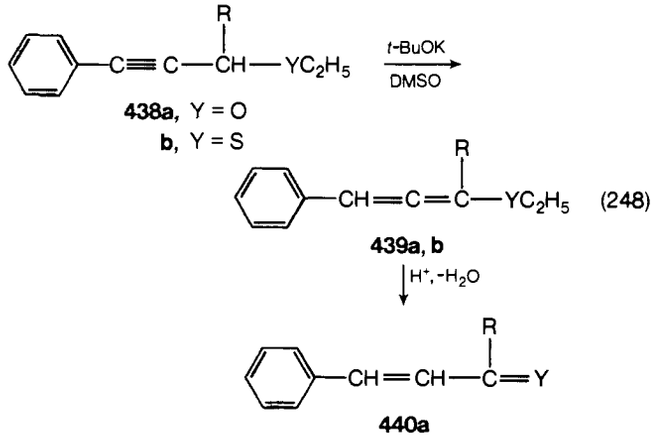
Smadja[215] in studying the heptynes found that the products formed from 1-heptyne (**434**) varied with the concentration of the *tert*-butoxide, the temperature, and the time. Usually the main product was the 2-isomer **435** (eq 246), although the 3-isomer could be produced in amounts as high as 40%.



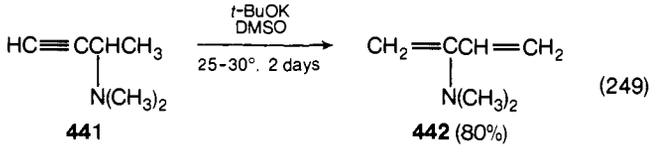
Propargyl ethers (**436**) yield the isomeric allenyl ether[240] **437** (eq 247). Former efforts to effect this trans-



formation with sodamide or KOH were unsatisfactory. Mantione[241] carried out this reaction with 3-alkoxy- (**438a**) and 3-alkylthio-1-phenylpropynes (**438b**) (eq 248). When Y = O, the allenyl ethers **439a** were converted into the cinnamyl ketones **440a** in yields of 40–67%; the allenyl thioethers **439b** (Y = S), resistant to hydrolysis, were obtained in yields of 60–80%.



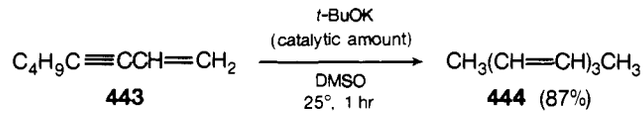
3-Dimethylamino-1-butyne (**441**) formed 2-dimethylamino-1,3-butadiene[239] (**442**). This method represents a useful synthesis (eq 249) of 2-dialkylamino-1,3-buta-



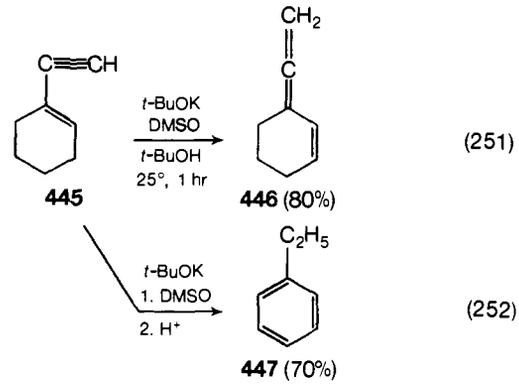
dienes since the substrate is available from acetylene and secondary amines.

F. Enynes and Diynes

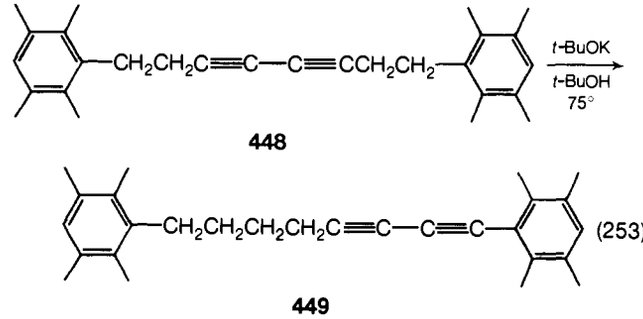
Conjugated enynes may lead to conjugated trienes.[236] Thus oct-1-en-3-yne (**443**) leads to 2,4,6-octatriene (**444**) (eq 250). In the case of conjugation which involves a



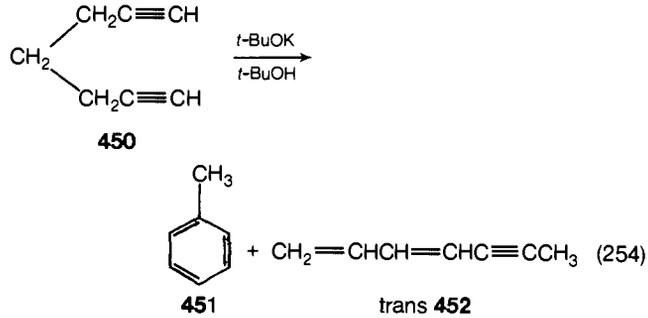
double bond in a six-membered ring, as in 1-ethynyl-1-cyclohexene (**445**), a vinylidene cyclohexene (**446**) is formed (eq 251). Mantione[242] in the same reaction using a large excess of DMSO followed by acidification obtained ethylbenzene (**447**) (eq 252).



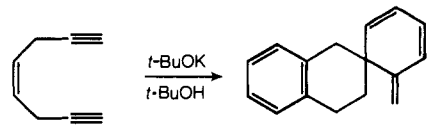
Diynes, such as 1,8-(bis-2,3,5,6-tetramethylphenyl)-3,5-octadiyne (**448**), isomerize quantitatively with the *tert*-butoxide to the 1,3-isomer[243] **449** (eq 253). On the



other hand, 1,6-heptadiyne (**450**) leads to toluene (**451**) and *trans*-1,3-heptadien-5-yne (**452**), in a 1:1 ratio[244] (eq 254).

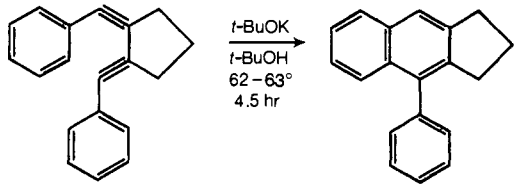


Further variation is illustrated in *cis*-4-octene-1,7-diyne (**453**) and 1,7-diphenyl-1,6-heptadiyne (**455**). The former cyclizes largely to the spiro compound[245] **454** (eq 255), while the latter cyclizes to 4-phenyl-2,3-dihydro-1*H*-benz[*f*]indene (**456**)[246] (eq 256).



(255)

453 454 (25%)

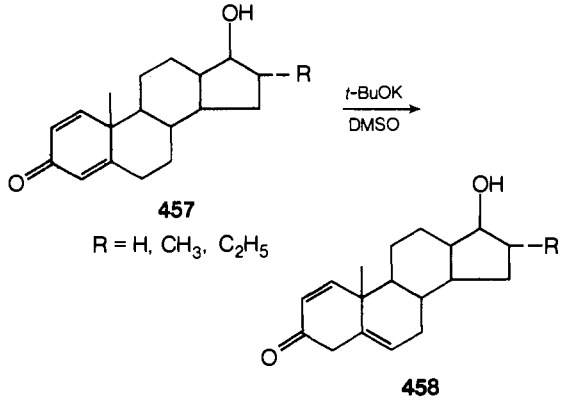


(256)

455 456 (35%)

G. Steroids

In the steroid series the *tert*-butoxide has been employed to remove conjugation in the A ring.[247] With this base $\Delta^{1,4}$-3-keto steroids **457** may be converted directly into $\Delta^{1,5}$-3-keto steroids **458** (eq 257). Sodium acetylide

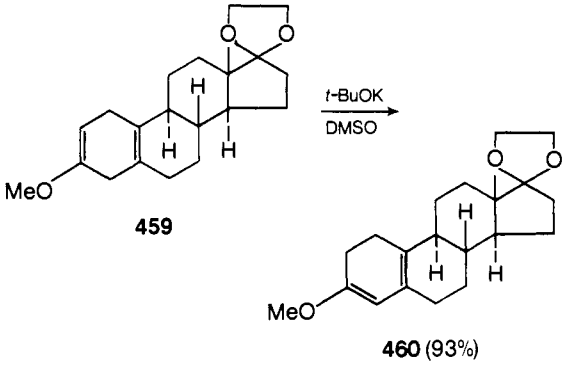


457
R = H, CH_3, C_2H_5

458

(257)

in DMSO, NaH, or $NaNH_2$ in THF also effect this isomerization. It is interesting to note that the product is so unstable that it may revert to the original during the workup. As might be expected it is also possible to introduce conjugation into the A ring. Thus Birch and coworkers[248] converted the 1,4-dihydro estrone **459** into the 1,2-isomer **460** (eq 258).



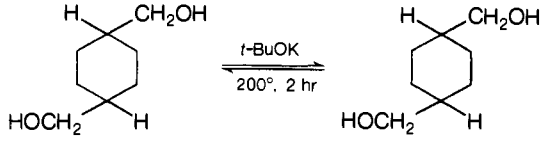
459

460 (93%)

(258)

H. Cis–Trans Isomerism

Although base-catalyzed isomerization usually involves an equilibrium between unsaturated compounds, such is not always the case. It may involve an equilibrium between the cis and trans forms of a cyclic type[249] (eq 259). In this case isomerization may well proceed *via* the aldehyde.

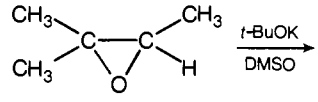


(60% trans) (74–76% trans)

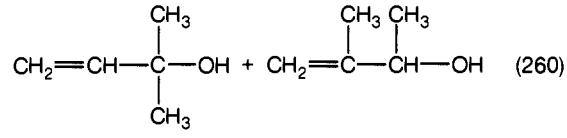
(259)

I. Isomerism Involving Heteroatoms

Isomerism may occur between an epoxide and an unsaturated alcohol. For example, tri- (**461**) and tetramethylethylene oxides (**464**) isomerize[250] under the influence of the *tert*-butoxide to give the allyl alcohols **462**, **463**, and **465**, respectively (eq 260 and 261). Ethylene oxide and its less substituted derivatives polymerize.

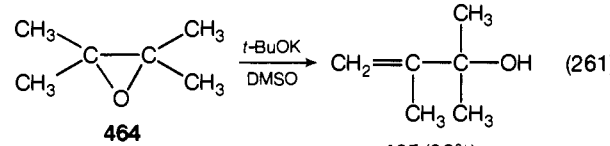


461



462 (80%) 463 (15%)

(260)

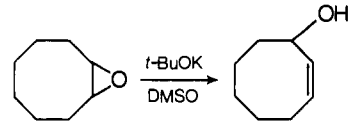


464

465 (98%)

(261)

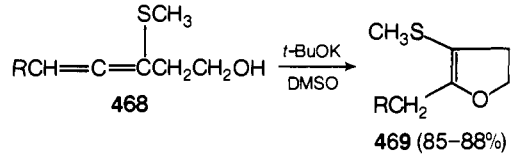
On the other hand, cyclooctene oxide (**466**) yields the allylic alcohol[251] **467** (eq 262). Lithium orthophosphate gives a 70% yield.



466 467 (46%)

(262)

Somewhat similarly 1-alkoxy- or 1-methylthio-1-(α- or β-hydroxyalkyl)allenes as **468** yield dihydrofurans[252] (**469**) (eq 263).

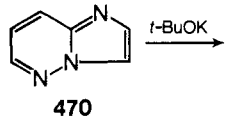


468

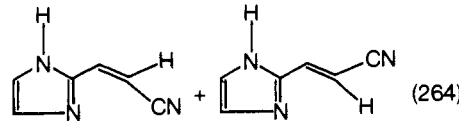
469 (85–88%)

(263)

Imidazo[1,2-*b*]pyridazine (**470**) was cleaved by the *tert*-butoxide to give the cis (**471**) and trans imidazoles (**472**) in a 3:1 ratio, respectively (eq 264). By contrast,



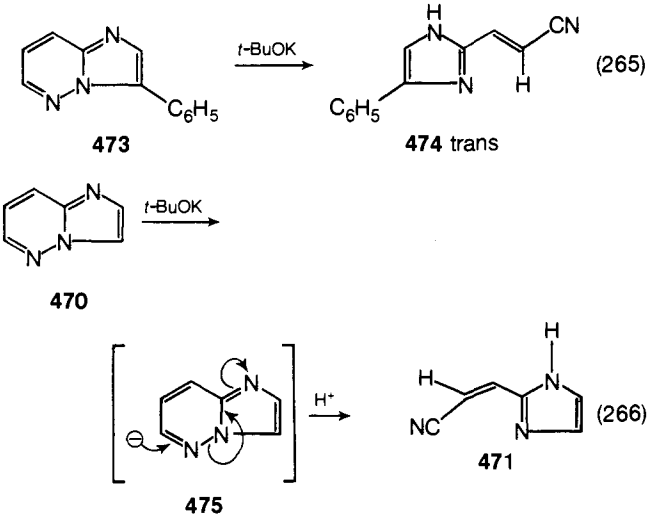
470



471 cis 472 trans

(264)

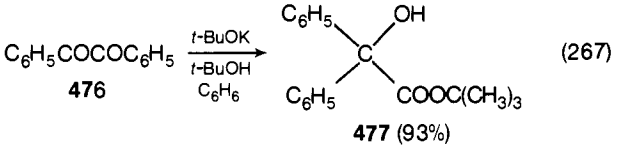
2-phenylimidazo[1,2-*b*]pyridazine (**473**) gives only the trans imidazole (**474**) (eq 265). The mechanism appears to involve the carbanion **475** (eq 266).



IX. Rearrangements

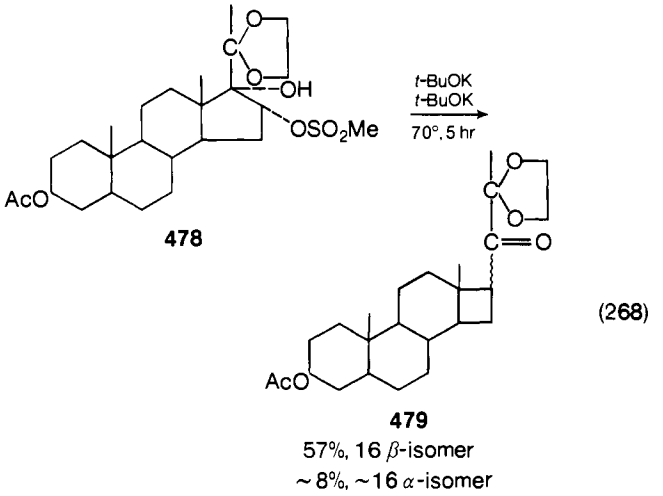
A. Benzils

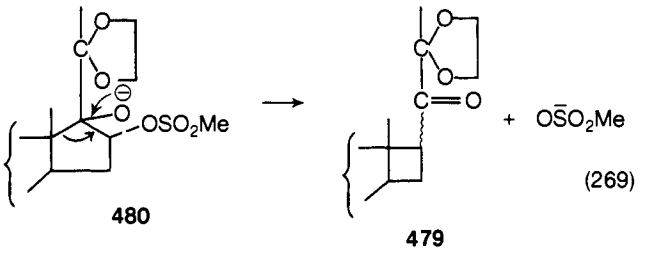
One of the earliest rearrangements with the use of the *tert*-butoxide was that of benzil[254] (**476**) to give the benzilic acid ester **477** (eq 267). Two conditions are essential for success: (a) the base must be sufficiently strong to effect the rearrangement; and (b) the structure involved must be such that the Meerwein–Ponndorf–Verley–Oppenauer equilibration is minimized or eliminated (see Oppenauer oxidation, section X.B.1). The yield with *tert*-butyl alcohol alone as solvent was 76%; with benzene alone, 90%. Sodium methoxide gave lower yields and no ester was obtained with $NaOC_2H_5$–C_2H_5OH.



B. Ketal of 5α-Pregnan-3β-ol-16-mesyl-17-hydroxy-20-one Acetate

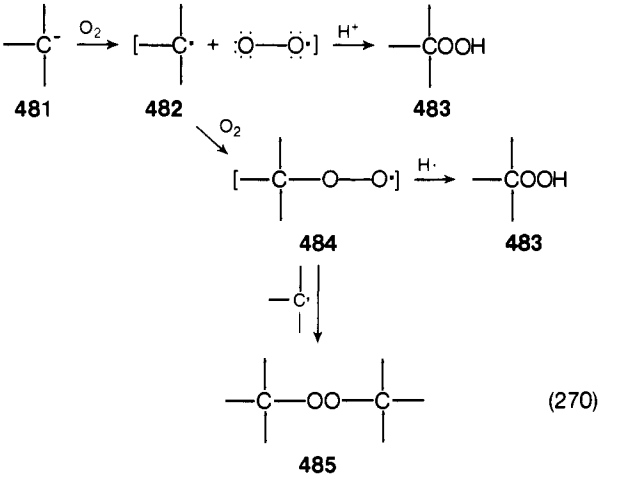
Although the contraction of a five- to a four-membered ring is not common, such has been accomplished by Ghera[255] in the synthesis of the *D*-norsteroid **479** from the methanesulfonate **478** (eq 268). The mechanism is possibly that of the pinacol rearrangement (eq 269) in which the anion **480** rearranges to give **479** with the elimination of $^-OSO_2Me$. If the mechanism is that of the pinacol rearrangement, it is unusual in being carried out in a basic medium.





X. Redox Reactions

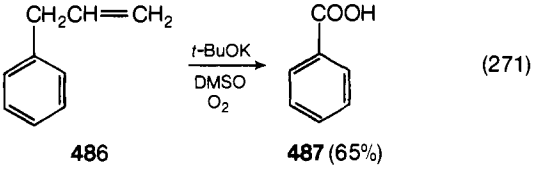
The purpose of the *tert*-butoxide in oxidation is to provide a large concentration of accessible carbanion **481** which is easily oxidized to a free radical (**482**) and then to a peroxide (**483**), or the free radical (**482**) may be oxidized to a peroxide free radical (**484**) which gives the peroxides **483** and **485** (eq 270). Further oxidation may then occur to form a carbonyl or carboxyl group depending on whether the initial carbanion was secondary or primary.



A. Oxidation in the Presence of Oxygen

1. Alkenes

Barton and Jones[256] oxidized a variety of organic compounds, mostly unsaturated aromatic, with the *tert*-butoxide in the presence of oxygen. The most common oxidation product, as shown for allylbenzene (**486**), was benzoic acid (**487**) (eq 271).



2. Mercaptans, Sulfides, Disulfides, and Sulfoxides

It has already been shown (section VII.E.5) that certain sulfoxides with the *tert*-butoxide undergo elimination to give good yields of alkenes. Many sulfur compounds also undergo base-catalyzed oxidation in the presence of oxygen or air, but the products and yields vary so greatly that the use of the reaction in synthesis would be limited. It is interesting to note that the rate of oxidation of *n*-butyl mercaptan has been determined.[257] In *tert*-butyl alcohol the rate ($K \times 10^3$, min^{-1}) was found to be 21.0 with *t*-BuONa, 34.7 with *t*-BuOK, 193 with *t*-BuORb, and 479 with *t*-BuOCs.

Typical reactions with a mercaptan (**488**), a disulfide (**489**), a sulfide (**490**), and two sulfoxides (**491** and **492**) are given in eq 272, 273, 274, 275, and 276, respectively. The most common product in these oxidations is benzoic acid (**487**).

$$\underset{\mathbf{488}}{C_6H_5CH_2SH} \xrightarrow[t\text{-BuOK}]{O_2,\ t\text{-BuOH},\ DMSO} \underset{\mathbf{487}\ (85\ mol\ \%)}{C_6H_5COOH} + \underset{(10\ mol\ \%)}{(C_6H_5CH_2)_2S}^{258} \quad (272)$$

$$\underset{\mathbf{489}}{(C_6H_5CH_2)_2S} \xrightarrow[DMSO]{O_2,\ t\text{-BuOH}} \underset{\mathbf{487}\ (70\ mol\ \%)}{C_6H_5COOH} + \underset{(18.4\ mol\ \%)}{C_6H_5CH{=}CHC_6H_5}^{258} \quad (273)$$

$$\underset{\mathbf{490}}{C_6H_5CH_2SCH_3} \xrightarrow[HMPA]{O_2,\ t\text{-BuOK}} \underset{\mathbf{487}\ (77\%)}{C_6H_5COOH} + \underset{(73\%)}{CH_3SO_2OH}^{259} \quad (274)$$

$$\underset{\mathbf{491}}{C_6H_5SOCH_3} \xrightarrow[HMPA]{O_2,\ t\text{-BuOK}} \underset{(86.4\ mol\ \%)}{C_6H_5SO_3H}^{260} \quad (275)$$

$$\underset{\mathbf{492}}{C_6H_5CH_2SOCH_2C_6H_5} \xrightarrow[HMPA]{O_2,\ t\text{-BuOK}} \underset{\mathbf{487}\ (88\ mol\ \%)}{C_6H_5COOH} + \underset{24\ mol\ \%}{C_6H_5CH{=}CHC_6H_5}^{260} \quad (276)$$

3. Ketones and Esters (to Hydroperoxides)

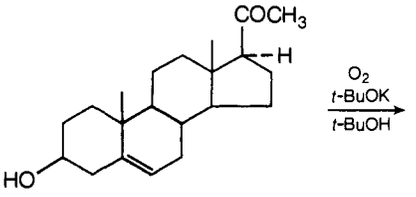
The oxidation (with oxygen) of ketones and esters to hydroperoxides has been accomplished with the *tert*-butoxide in an aprotic solvent at low temperature.[261] Highest yields from ketones are favored with (a) an excess of the *tert*-butoxide; (b) short reaction times; (c) low temperature (<−8°); and (d) the use of polar aprotic solvents, DME and DMF. Typical ketone (**493**) and ester (**495**) oxidations to the hydroperoxides **494** and **496** are found in eq 277 and 278, respectively.

$$\underset{\mathbf{493}}{(CH_3)_2CHC(=O)CH(CH_3)_2} \xrightarrow[DMF]{O_2,\ t\text{-BuOK}} \underset{\mathbf{494}\ (93\%)}{(CH_3)_2CHC(=O)C(OOH)(CH_3)CH_3} \quad (277)$$

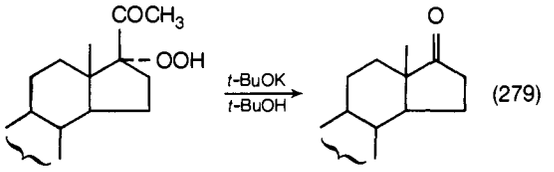
$$\underset{\mathbf{495}}{C_6H_5CH(H)COOC(CH_3)_3} \xrightarrow[DME]{O_2,\ t\text{-BuOK}} \underset{\mathbf{496}\ (55\%)}{C_6H_5CH(OOH)COOC(CH_3)_3} \quad (278)$$

Barton and coworkers[262] converted 3β-hydroxypregn-5-en-20-one (**497**) into the hydroperoxide **498** which in turn was converted into 3β-hydroxyandrost-5-en-17-one (**499**) by Siddall and coworkers[263] (eq 279). The final product[263] (7.4 g) may also be produced in one operation from **497** (10 g) by treatment with O_2, *t*-BuOK, *t*-BuOH, and THF, a fact which indicates that **498** is an intermediate in the formation of **499**.

Barton and coworkers[264] employed the hydroperoxide **500** obtained from steroidal 20-ketones without a substituent at C-17 or C-21 for the synthesis of 17-hydroxy steroids **501** in good yield (eq 280). This conversion from

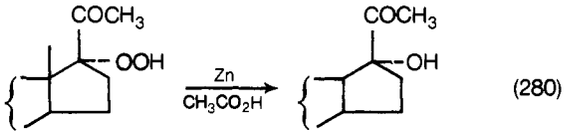


497



(279)

498 (45%) **499** (80%)



(280)

500 **501**

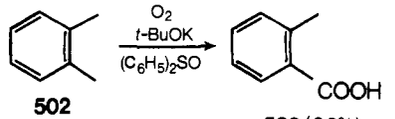
the original ketone has now been improved in a one-step process by employing *t*-BuONa, *t*-BuOH, DMF, and triethyl phosphite (as the reducing agent).[265] Upon hydrolysis the α-ketol is obtained in yields as high as 65%. In a similar manner[262] a 6-oxo-5α-steroid may be converted into a 5α-hydroxy-6-ketone.

4. Ketones (to Acids)

Schriesheim and coworkers[266] found that the *tert*-butoxide in HMPA with oxygen near room temperature gave a better yield (88%) of benzoic acid from acetophenone than bases such as LiOH, NaOH, or KOH in the same solvent.

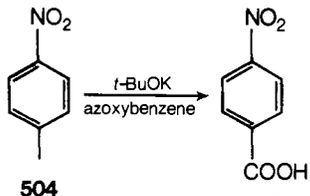
5. Methylarenes and Picolines

Wallace and coworkers[267a] found that o-xylene (**502**) could be oxidized with oxygen in the presence of the *tert*-butoxide to toluic acid (**503**) (eq 281), while *p*-nitrotoluene (**504**) gave *p*-nitrobenzoic acid[267b] (**505**) in quantitative yield (eq 282). Only readily acidic hydrocarbons are affected. Potassium hydroxide substituted for the *tert*-butoxide at 80° led to no oxidation product.



(281)

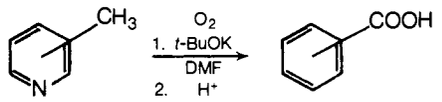
502 **503** (92%)



(282)

504 **505**

The picolines **506** (eq 283) were oxidizable to the corresponding carboxylic acid[268] **507**. There was no measurable oxidation when *tert*-butyl alcohol was substituted for DMF.

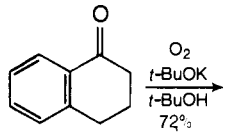


(283)

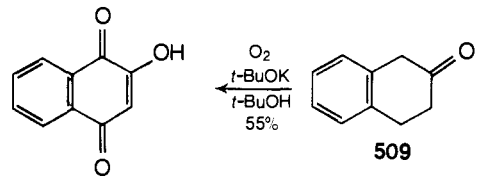
506 **507** (~quantitative)

6. Ketones and 1,2-Dihydroxynaphthalenes

α- (**508**) and β-tetralones (**509**) and 1,2-dihydroxynaphthalene with oxygen and the *tert*-butoxide are converted into 2-hydroxy-1,4-naphthoquinone[269] (**510**) (eq 284). Since both tetralones give the same product, the common intermediate, according to Bailie and Thomson, must be the α-diketone. Thus the oxidation represents a general method for preparing these hydroxyquinones.



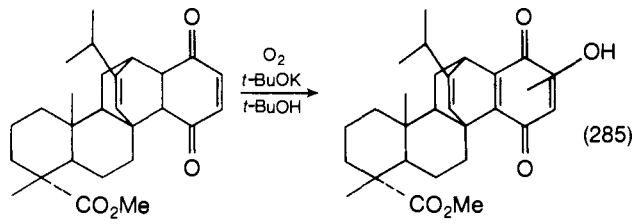
508



(284)

510 **509**

The method has been applied to more complicated ring types, such as the adduct formed from the methyl ester of levopimaric acid and benzoquinone[270] (**511**), which oxidizes to the hydroxyquinone **512** (eq 285). The exact location of the hydroxyl group in the product was not determined.

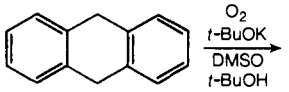


(285)

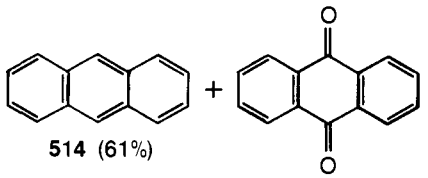
511 **512** (20%)

7. Hydroaromatic Hydrocarbons

Barton and Jones[271] in treating dihydroanthracene (**513**) with the *tert*-butoxide in the presence of oxygen obtained anthracene (**514**) and anthraquinone (**515**) (eq 286).



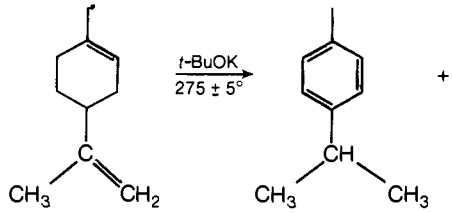
513



(286)

514 (61%) **515** (17%)

A similar dehydrogenation of the ring in limonene (**516**) to obtain *p*-cymene (**517**) was accomplished by



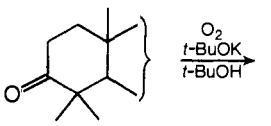
(287)

516 **517** (95%)

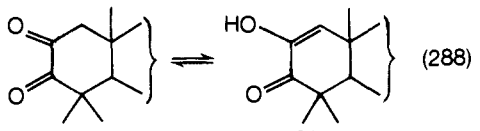
Pines and Schaap[272] except that nitrogen rather than oxygen was present over the reaction mixture and the *tert*-butoxide alone was the reagent (eq 287). The *tert*-butoxide in this high-pressure reaction was much more effective than alkoxides of primary and secondary alcohols.

8. Steroidal 3-Ketones

Hanna and Ourisson[273] were successful in oxidizing, with air in the presence of the *tert*-butoxide, the 3-ketones **518** in the dimethyl-4,4-cholestane, in the dipterocarpol, in the dimethyl-4,4-cholestane-5, and in the lupane series to the 2,3-diketones **519**. The oxidation affecting ring A (**518**) in each case is given in eq 288, in



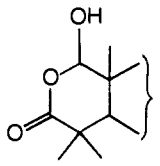
518



(288)

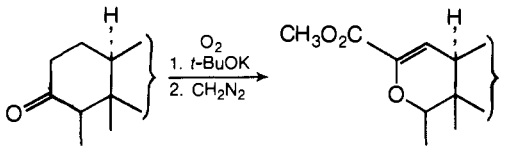
519 **520**

which **519** is in equilibrium with its enolic form (**520**). In some cases the lactol **521** is obtained as well.



521

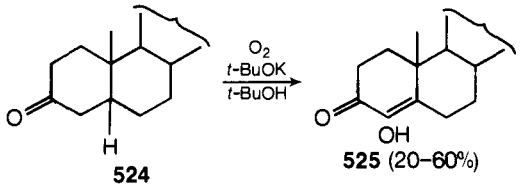
In the application to friedelin (**522**),[274] the oxidation gives not a 2,3-diketone but an unsaturated ester (**523**) (eq 289).



(289)

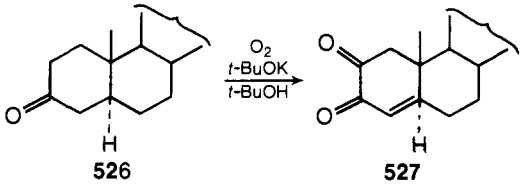
522 **523**

In addition Camerino and coworkers[275] did not obtain 2,3-diketones exclusively in the oxidation of a series of 3-keto steroids with no substituents in position 4. From 3-keto-5β-steroids (**524**) these investigators obtained 4-hydroxy-Δ^4-3-ketones (**525**) (eq 290). 3-Keto-5α-steroids (**526**) gave the enolic form of the 2,3-diketo derivative **527** (eq 291), and Δ^4-cholesten-3-one (**528**) yielded the diosterol-I (**529**) (eq 292).



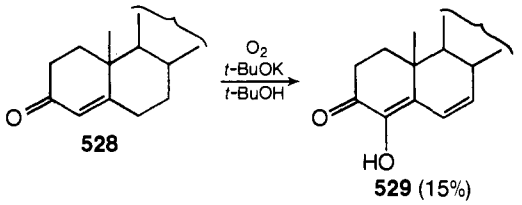
(290)

524 **525** (20–60%)



(291)

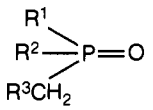
526 **527**



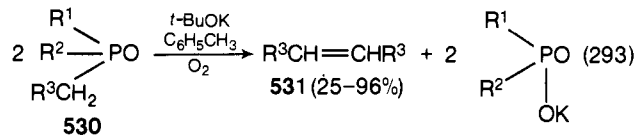
528 529 (15%) (292)

9. Phosphine Oxides or Alkylphosphonic Acid Esters (to Symmetrical Alkenes)

A variety of stilbenes have been synthesized, by using the *tert*-butoxide and oxygen, from phosphine oxides or alkylphosphonic acid esters of the type[276]



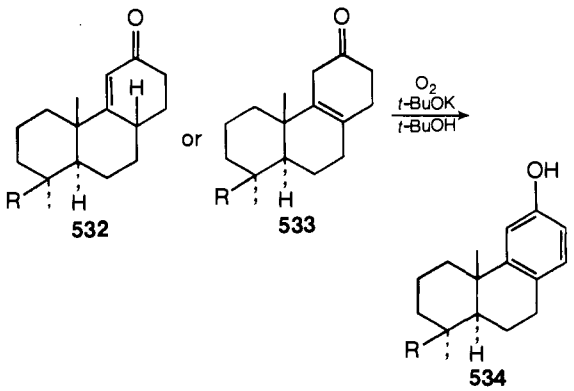
where R^1 and R^2 = aryl or ethoxy groups and R^3 = an aryl group. In the reaction for the type **530**, elimination occurs to give the stilbene **531** (eq 293).



530 531 (25–96%) (293)

10. Ketones (to Phenols)

In an attempt to prepare the hydroperoxide Crowshaw and coworkers[277] treated the ketones available from *O*-methylpodocarpic acid (**532** and **533**) with oxygen and the *tert*-butoxide. They obtained not the hydroperoxide, but instead a phenol (**534**) (eq 294). The hydroperoxide available by another method was shown not to be an intermediate.

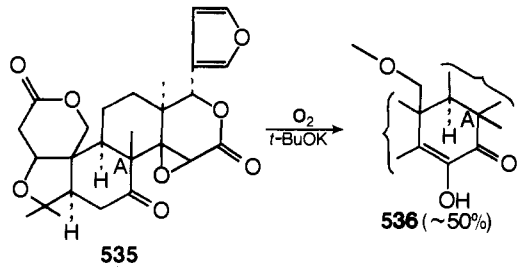


532 533 534 (294)

R = COOH, CO_2Me, CH_2OH

11. Limonin (to Diosphenol)

Oxidation with oxygen has also been employed to obtain diosphenol (**536**) from limonin[278] (**535**) (eq 295). The method is a most useful one for preparing diosphenols.

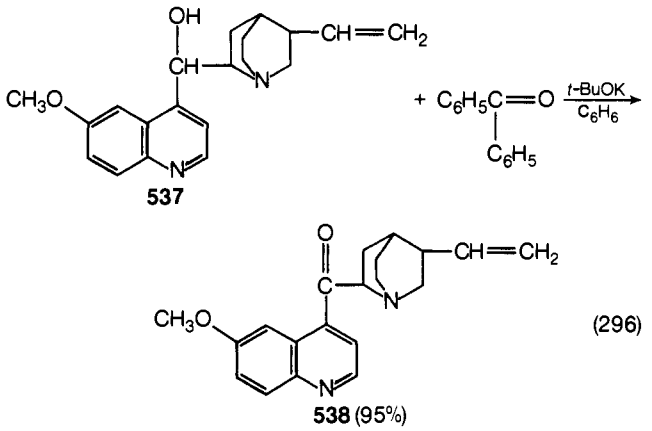


535 536 (~50%) (295)

B. Oxidation and Reduction by Hydride Transfer

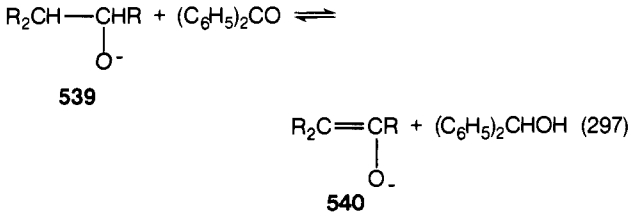
1. Oppenauer

The Oppenauer oxidation is a common procedure for preparing ketones from alcohols. With amino alcohols the usual reagent (aluminum alkoxide and a ketone) is unsatisfactory since the alkoxide complexes with the amino group of the alcohol. To overcome this difficulty, the *tert*-butoxide with benzophenone in benzene has been employed[279] (eq 296). Not only may quinine (**537**) as shown



537 538 (95%) (296)

be oxidized to quininone (**538**), but quinidine, dihydroquinidine, dihydrocinchonine, dihydrocodeine, dihydromorphine, and dihydrothebainol have been oxidized satisfactorily to the corresponding ketones. The success of the procedure is attributed to the ability of the alcohol to exist as an anion (**539**) which in the presence of benzophenone forms an enol (**540**) whose potassium salt[279a] (eq 297) is stable.

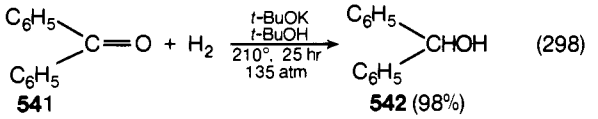


539 540 (297)

More recently Warnhoff and Reynolds-Warnhoff[280] by substituting fluorenone for benzophenone have found that the reaction can be carried out satisfactorily at room temperature in 0.5 to 1 hr, although our experience indicates that the product is cleaner if the time is extended to 6 days at room temperature with the addition of more fluorenone.[281]

2. Benzophenone (Homogeneous Catalysis)

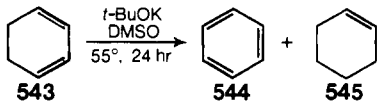
Walling and Bollyky[282] hydrogenated benzophenone (**541**) to benzhydrol (**542**) by using the *tert*-butoxide as a homogeneous catalyst (eq 298). The reaction is thought to occur *via* a hydride ion intermediate. Acetone and cyclohexene were not affected under similar conditions.



541 542 (98%) (298)

3. 1,3-Cyclohexadiene (Disproportionation)

Schriesheim and coworkers[283] found that 1,3-cyclohexadiene (**543**) with the *tert*-butoxide was converted into benzene (**544**) and cyclohexene (**545**) quantitatively (eq 299). The kinetics of the reaction indicate that a hydride transfer is the rate-determining step.



543 544 545 (299)

C. Reduction

1. 1,3-Pentadiene (Selective Hydrogenation)

Slaugh[231b] succeeded in half-hydrogenating 1,3-pentadiene (**546**), in the presence of the *tert*-butoxide and NaH, to 1-pentene (**547**) (eq 300). Sodium hydride alone promotes the reaction, but the *tert*-butoxide alone does not. The *tert*-butoxide, however, enhances considerably the catalytic activity of the hydride.

$$\underset{\textbf{546}}{CH_3CH{=}CHCH{=}CH_2} + H_2 \xrightarrow[\text{NaH}]{t\text{-BuOK}} \underset{135°,\ 0.1\ hr}{} \quad (300)$$

$$CH_3CH_2CH_2CH{=}CH_2 \ (\textbf{547},\ 56.5\%) + \text{dimer}\ (25.7\%)$$

2. Wolff–Kishner

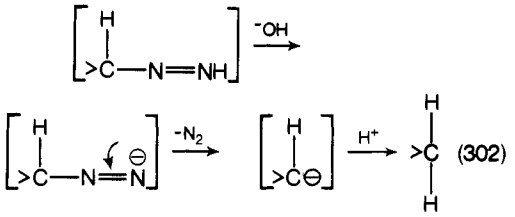
The Wolff–Kishner reaction is a common procedure for converting an aldehyde or ketone into a hydrocarbon. In the first step the carbonyl compound is transformed into a hydrazone which is usually converted into the hydrocarbon by heating with an alkali such as KOH. Cram and coworkers[284] discovered that the hydrazone **548** may be reduced to the hydrocarbon **549** at room temperature with the *tert*-butoxide (eq 301). Yields with four hydrazones vary from 64 to 90%. Later Grundon and coworkers[285] employed the *tert*-butoxide in toluene at higher temperature with yields from three hydrazones varying from 65 to 85%. The mechanism involves the carbanion **550** (eq 302). The equations demonstrate that along with the base a protonic source is absolutely necessary.[286]

$$ArCOAr \xrightarrow{NH_2NH_2} \underset{\underset{NNH_2}{\|}}{ArCAr} \xrightarrow[DMSO,\ 25°]{t\text{-BuOK}} \underset{\textbf{549}}{ArCH_2Ar} \quad (301)$$

548

$$>C{=}NNH_2 \xrightarrow{^-OH} [>C{=}\bar{N}NH \leftrightarrow >\bar{C}{-}N{=}NH] \xrightarrow{H^+}$$

550



(302)

3. α,β-Unsaturated Ketones (Selective Reduction)

The reduction of α,β-unsaturated ketones to saturated ketones has been discussed under Isomerization (section VIII.C).

XI. Summary and Conclusion

Potassium *tert*-butoxide, with its variable basicity and relatively poor tendency to add to unsaturated electrophiles, has proved to be a versatile proton abstractor. For reactions which require a strong proton abstractor [Elimination (VII), Isomerization (VIII), or other transformations involving a substrate with an acidity even as low as toluene (deuterium exchange (II.B))] potassium *tert*-butoxide in DMSO has many attractive features. It should be kept in mind that this mixture consists of *tert*-butoxide and dimsyl anions[12] and that its basicity is dependent on the purity of the *tert*-butoxide and the exclusion of water from DMSO.

It is thought that to obtain the most basic form of the *tert*-butoxide it is necessary to break down the aggregate which exists in protic or nonpolar solvents to a monomeric or nearest to a monomeric butoxide anion. This can be done best by the addition of reagents, such as DMSO or crown ethers, which act as ligands for the cation. Differences in behavior of the clustered and monomeric or less clustered forms of the *tert*-butoxide anion have been utilized in the selective synthesis of either the cis or trans forms of some alkenes (section VII.C.1). For reactions which require a relatively weaker proton abstractor [Aldolization (V) and some Acylations (VI)], the *tert*-butoxide in its own alcohol, in THF, or in benzene may offer certain advantages, particularly in ring closure. However, regardless of the reaction attempted, the base should be the weakest one which will effect the abstraction in order to make the reaction as selective as possible. The choice may well range among the various forms of the *tert*-butoxide, but in extreme circumstances it may include either stronger bases such as lithium diisopropylamide or *tert*-butyllithium, or weaker ones such as 2,6-di-*tert*-butylphenoxide. All these bases cover an extraordinary range of activity for proton abstraction. Proper choice of base in a synthesis may determine the difference between success and failure. Enough examples are given in the review to indicate the type of base required for various reactions or substrates.

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